Clinical Protocol
for the
BIO-Precision Study

Assessment of the utility of BIOMONITOR to identify atrial fibrillation (AF) in ablation candidates using precise AF detection

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PROTOCOL SIGNATURE PAGE

The signature below constitutes the receipt and review of the BIO-Precision Clinical Study protocol and any attachments, and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations, ICH, and GCP guidelines.

STUDY SITE PRINCIPAL INVESTIGATOR:

Signed: _____

Name (please print)

_____ _____

Signature Date

SUMMARY

Title	BIO-Precision Study
Descriptor	Assessment of the utility of BIOMONITOR to identify AF in ablation candidates using precise AF detection
Design	Prospective, multicenter, observational study
Purpose	The purpose of this study is to evaluate the diagnostic utility of BIOTRONIK's subcutaneous cardiac rhythm monitor (SCRM) for the detection of AF prior to an ablation procedure.
Subject Population	Study population includes patients diagnosed with paroxysmal AF being evaluated for an AF ablation.
Sample Size	This study will enroll up to 100 subjects, to obtain 60 usable Holter recordings.
Clinical Sites	Up to 5 U.S. sites.
Follow-up Period	All subjects will be followed for three months post 48 hr Holter monitoring.
Primary Objective	The primary objective of this study is to determine the diagnostic utility of the BIOMONITOR to detect AF within study subjects who are being evaluated for an ablation. Specifically, the diagnostic sensitivity of the BIOMONITOR will be determined by comparing AF events detected by the BIOMONITOR and 48 hr Holter monitor for each subject. Using the 48 hr Holter monitor as the gold standard, subjects with AF events detected by the BIOMONITOR will be categorized as true positive or false positive.
Study Risk Determination	Standard of care study including market released devices implanted according to FDA approved indications for use.
Sponsor	BIOTRONIK, Inc. Clinical Studies Department 6024 SW Jean Road Lake Oswego, Oregon 97035

1. INTRODUCTION

1.1 Study Overview

BIO-Precision is a post-market study investigating the utility of atrial fibrillation (AF) detection using BIOTRONIK's subcutaneous cardiac rhythm monitor (SCRM). The purpose of this study is to evaluate the diagnostic utility of BIOTRONIK's SCRM for the detection and confirmation of AF prior to an ablation procedure. Study population includes patients with paroxysmal AF being evaluated for an AF ablation. This study will enroll up to 100 subjects, to obtain 60 usable Holter recordings, at 5 study sites within the United States (U.S.). Study subjects will be followed for three months after the completion of a 48 hr Holter monitor.

1.2 Background

SCRMs are devices capable of long-term cardiac rhythm monitoring. These devices are commonly used to assist in the diagnosis of unexplained palpitations and syncope. SCRMs provide more reliable and accurate monitoring than a routine surface ECG and can provide continuous long term monitoring compared to Holter monitoring. A growing use of SCRMs is for the detection and management of AF, in particular in patients with high thromboembolic risk. SCRMs were originally designed after pacemaker technology, however, current SCRMs have significantly decreased profiles, allowing for less-invasive insertion procedures[1] and low complication rates,[2,3] making them a safe and efficient option for arrhythmia diagnosis.

Atrial fibrillation is the most common diagnosed arrhythmia, and it is estimated to effect 6-12 million people in the U.S. by 2050.[4,5] AF has many causes and can be both symptomatic and asymptomatic, and is associated with an increase in hospitalizations, stroke, and heart failure.[6] Recent studies have suggested that the adverse effects of AF may be correlated with AF episode duration;[7] therefore it is important to appropriately capture AF episodes and their durations to adequately treat patients and reduce their AF burden.[8] AF can be diagnosed through medical history, exam, and a surface ECG; however, for non-sustained or paroxysmal AF, a surface ECG may not be sufficient to accurately detect the patient's true AF burden. Therefore, the use of a SCRM may result in precise and accurate AF detection over a longer period of time as compared to traditional surface (e.g. Holter) monitors.

Recent guidelines recommend AF ablation in patients with symptomatic AF, refractory or intolerant to at least one Class 1 or 3 antiarrhythmic medication. Asymptomatic patients may choose to pursue an AF ablation as an alternative to continuous, long-term anticoagulation therapy.[9] ECG monitoring is recommended pre- and post AF ablation procedure. Prior to undergoing an ablation, it is important for the physician to confirm the presence of AF as well as the current AF burden. Available methods for ECG monitoring, as discussed above, range from in office ECG, Holter (24 hours to 7 days), or SCRMs (up to 4 years of continuous arrhythmia monitoring). Not only are SCRMs valuable for detecting AF and AF burden prior to ablation, they may also provide important data post-ablation in

assisting the physician in determining the success rate of the ablation procedure. The focus of this study is to determine the utility of SCRMs for AF detection in patients who are being evaluated for an ablation.

1.2.1 BioMonitor Single-center AF Detect Study

BIOTRONIK conducted an AF Detection clinical study in order to assess the performance of the BioMonitor AF feature in clinical practice. This study used BIOTRONIK's first generation SCRM, which received FDA approval on June 2, 2014 (510(k) number: K132960). The ability of BioMonitor to detect episodes of AF was quantified in comparison with the gold-standard, expert-annotated, external Holter ECG recorder. Sixty six (66) participants with suspected paroxysmal or persistent atrial fibrillation who had been implanted with a BioMonitor were additionally equipped with an external Holter ECG recorder.

The main aim of the AF Detect study was to record surface electrocardiograms (ECG) to reference it with the subcutaneous ECG of the BioMonitor. For this reason a Holter ECG device was applied, and the patient was asked to come back after 2 days. All episodes were interrogated and a memory dump was conducted. The site was equipped with the long-term three channel Holter ECG system "LifeCard" from the company "Spacelabs Healthcare" (www.spacelabshealthcare.com). This is a CE-approved compact Holter Ambulatory ECG Recorder that is capable of storing a continuous, 48-hour recording of up to 3 leads onto a Compact Flash (CF) card. Lifecard ECG was used to establish an independent assessment of AF, and represents the gold standard for AF detection. The LifeCard ECGs were manually annotated for AF episode onset and termination, and the annotations were verified by an independent ECG reviewer.

The surface ECG of the Holter ECG and the subcutaneous ECG of the BioMonitor were synchronized by time and date and manually assessed to determine the AF detection performance. Furthermore, automatically detected arrhythmias were assessed and documented. BioMonitor and LifeCard AF episodes were directly compared to one another on an episode-by-episode basis, by which each episode longer than 2 minutes in duration (default BioMonitor confirmation window) was classified as true positive (TP), false positive (FP), or false negative (FN).

Of the 66 participants in AF Detect, 39 showed at least one true AF episode during the 48-hour Holter period, with a maximum of 30 distinct, true AF episodes experienced by one subject. A total of 146 AF episodes were annotated from 2878 hours of Holter ECG data. During the execution of the AF Detection study, three subjects had missing Holter data, and hence were excluded from the analysis. The primary endpoint analysis determined an AF detection sensitivity of 95.4% ± 13.3% and a positive predictive value of 76.3% ± 38.7%.[10]

1.3 System Description

This study utilizes BIOTRONIK's subcutaneous cardiac rhythm monitor (SCRM).

The BIOMONITOR is a SCRM that continuously monitors the heart rhythm. BIOMONITOR programming and data collection during insertion and follow-up are performed with a portable BIOTRONIK programmer. Additionally, the Home Monitoring feature enables physicians to perform remote diagnosis management over the lifetime of the device.

The BIOMONITOR records automatically the occurrence of certain cardiac arrhythmias.

The BIOMONITOR is indicated to detect the following cardiac arrhythmias:

- Atrial fibrillation
- Bradycardia
- Sudden rate drop
- High ventricular rate (HVR)
- Asystole

Devices included in the clinical study:

- BioMonitor 2 (FDA clearance April 11, 2016; K152995 number) or FDA cleared successor (hereafter, referred to as BIOMONITOR)

The BIOMONITOR is to be used with the following components:

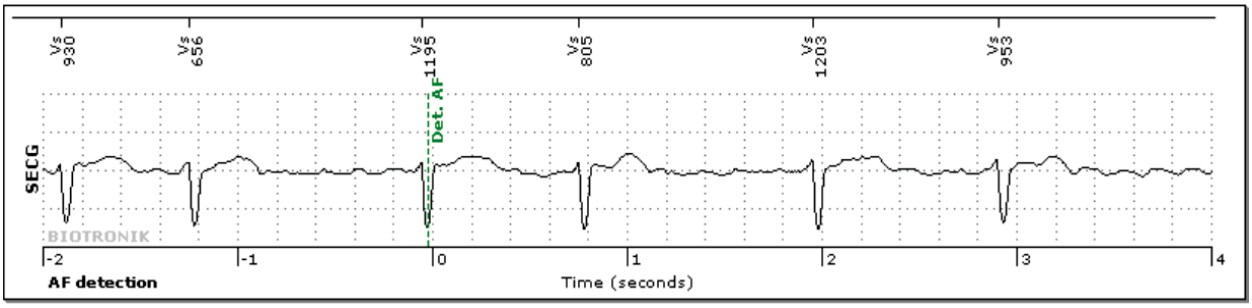
- BIOTRONIK Renamic or ICS 3000 programmer or FDA-cleared successor with the most recent software and later corresponding software updates

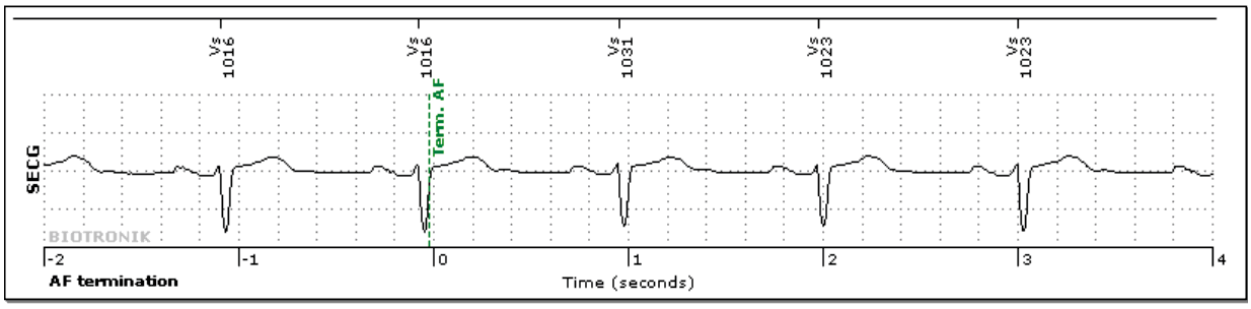
Subjects inserted with a BIOMONITOR will be remotely monitored with BIOTRONIK's Home Monitoring® system and will be provided a BIOTRONIK CardioMessenger II, II-S or FDA-cleared successor. The BIOTRONIK Remote Assistant may also be provided and allows manual triggering of an ECG recording by the patient.

1.3.1 BIOTRONIK Home Monitoring® with daily sECGs

The BIOTRONIK Home Monitoring® system provides early detection of arrhythmic events such as high ventricular rates and of silent, asymptomatic events like atrial fibrillation (Figure 1), through the transmission of detection and termination snapshots of the indicated event. Transmissions include both periodic and triggered subcutaneous electrocardiogram (sECG) recordings.

Figure 1: Atrial Fibrillation sECG Transmission Example





The BIOMONITOR has the capability to transmit messages including sECG signals to the BIOTRONIK Home Monitoring® Service Center daily so that the monitoring physician will have updated data on the technical and physiological parameters of the patient every 24 hours. BIOTRONIK Home Monitoring® can be used to provide the physician with advance reports from the BIOMONITOR and can process them into graphical and tabular format.

2. STUDY DESIGN

The BIO-Precision study is a post-market, multicenter, prospective, observational study designed to evaluate AF detection performance of BIOTRONIK's SCRM, BIOMONITOR. Up to 100 subjects will be enrolled to collect a total of 60 usable Holter recordings. The subject population includes patients that are diagnosed with paroxysmal AF and are being evaluated for an AF ablation procedure. Study subjects will be enrolled at up to 5 participating U.S. sites. Subjects will be followed for three months after the completion of 48 hr Holter monitoring.

Potential subjects will be identified by the investigator from their general patient population and must have an approved indication for continuous arrhythmia monitoring with an SCRM according to local regulations. Subjects will be consented no more than 14 days prior to the insertion procedure (Figure 2) and screened to ensure they meet all of the inclusion and none of the exclusion criteria. Subjects may also be screened and consented up to 30 days following the insertion of a BIOMONITOR (Figure 2). All subjects will be considered 'provisionally enrolled' until they initiate the 48 hr Holter monitoring, at which time they are considered fully enrolled.

For subjects with an existing BIOMONITOR, a pre-Holter observation period will be initiated at enrollment (Figure 2). This observation period should be 12-16 days in duration and will allow for characterization of the BIOMONITOR performance prior to Holter monitoring. Following this observation period, Holter monitoring should be initiated within 7 days. For subjects consented before BIOMONITOR insertion, the insertion procedure should be completed within 14 days, followed by the pre-Holter observation period (Figure 2). Holter monitoring should be initiated within 7 days after the completion of the observation period.

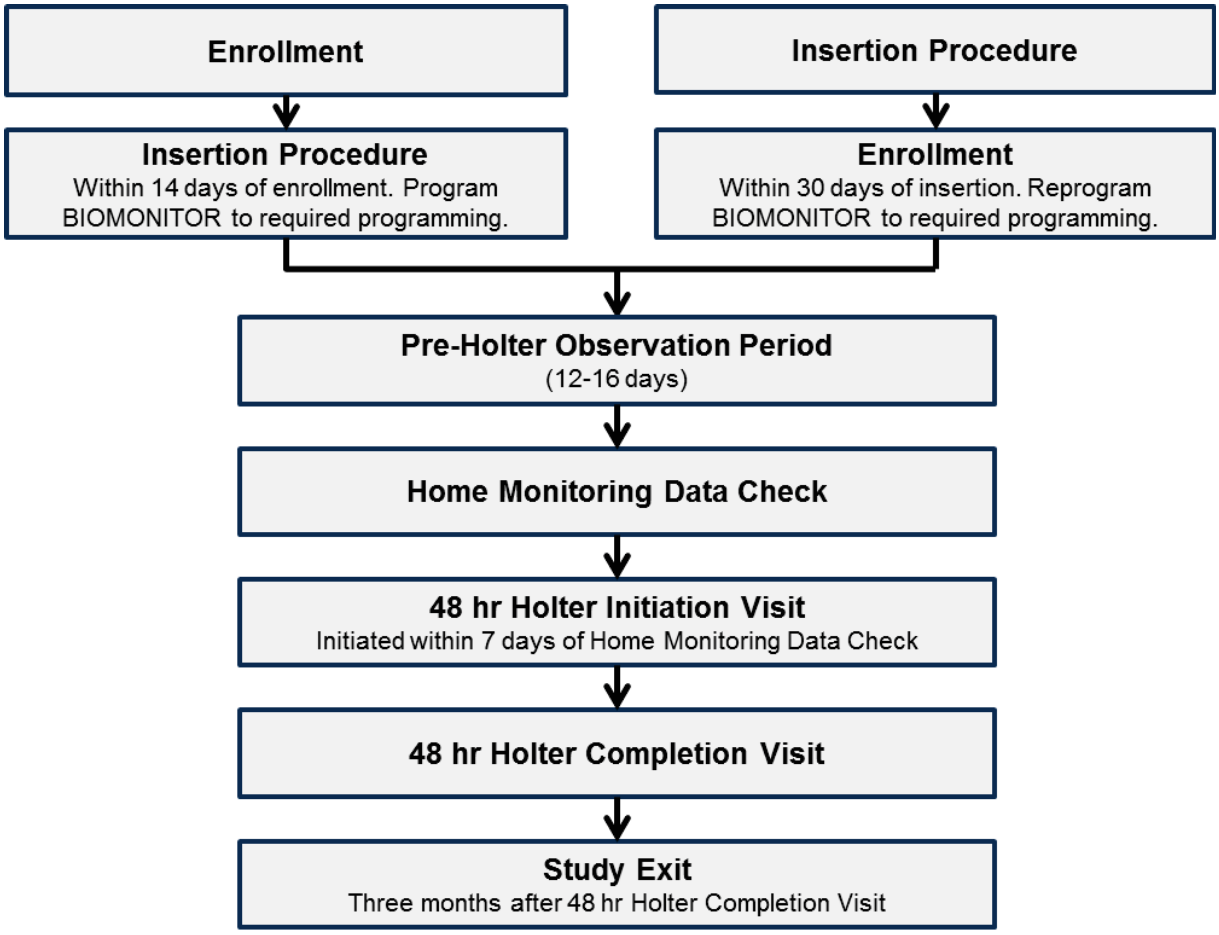
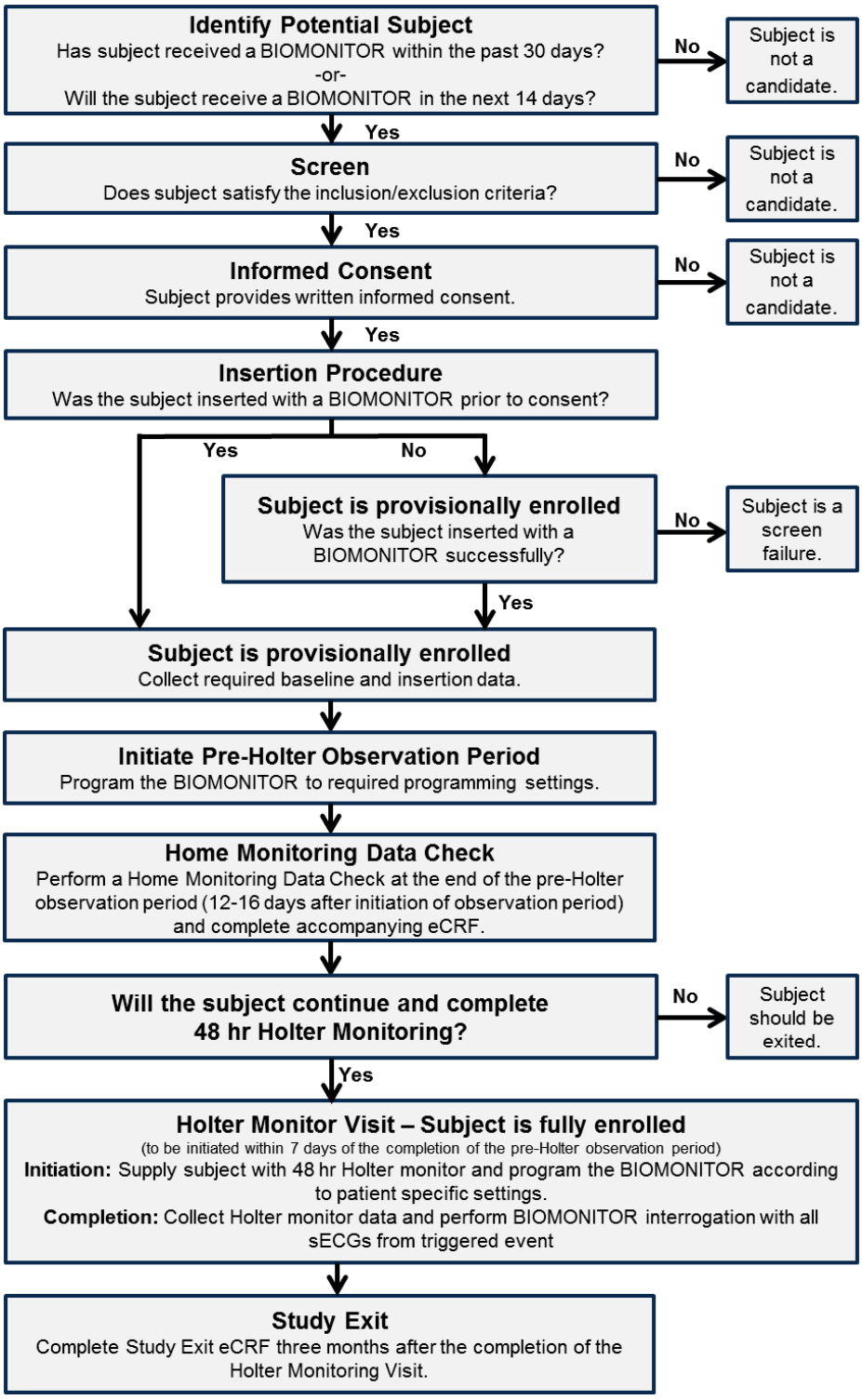


Figure 2: Enrollment Pre- and Post-BIOMONITOR insertion

The primary analysis will focus on the utility of the BIOMONITOR for the detection of AF within patients who are being evaluated for an ablation. Data will be collected from in-person visits at study enrollment, BIOMONITOR insertion, and initiation and completion of 48 hr Holter monitoring. In addition, BIOMONITOR performance data will be collected throughout the study duration using BIOTRONIK Home Monitoring®, including a required Home Monitoring data check at the end of the pre-Holter observation period. Holter monitor recordings will be evaluated by a Holter Core Laboratory. In addition, BIOMONITOR detections may be adjudicated by an event adjudication committee, if applicable.

Figure 3 provides an overview of the clinical study design. Details of subject eligibility requirements are noted in Section 3.2.2 and details of other study specific procedures and data collection are noted in Section 3.2 and Section 4.

Figure 3: BIO-Precision Study Design Flowchart


Identify Potential Subject
Has subject received a BIOMONITOR within the past 30 days?
-or-
Will the subject receive a BIOMONITOR in the next 14 days?
No
Subject is not a candidate.
Yes
Screen
Does subject satisfy the inclusion/exclusion criteria?
No
Subject is not a candidate.
Yes
Informed Consent
Subject provides written informed consent.
No
Subject is not a candidate.
Yes
Insertion Procedure
Was the subject inserted with a BIOMONITOR prior to consent?
Yes
No
Subject is provisionally enrolled
Was the subject inserted with a BIOMONITOR successfully?
No
Subject is a screen failure.
Yes
Subject is provisionally enrolled
Collect required baseline and insertion data.
Initiate Pre-Holter Observation Period
Program the BIOMONITOR to required programming settings.
Home Monitoring Data Check
Perform a Home Monitoring Data Check at the end of the pre-Holter observation period (12-16 days after initiation of observation period) and complete accompanying eCRF.
Will the subject continue and complete 48 hr Holter Monitoring?
No
Subject should be exited.
Yes
Holter Monitor Visit – Subject is fully enrolled
(to be initiated within 7 days of the completion of the pre-Holter observation period)
Initiation: Supply subject with 48 hr Holter monitor and program the BIOMONITOR according to patient specific settings.
Completion: Collect Holter monitor data and perform BIOMONITOR interrogation with all sECGs from triggered event
Study Exit
Complete Study Exit eCRF three months after the completion of the Holter Monitoring Visit.

2.1 Study Objectives

This study includes the assessment of one primary objective related to the diagnostic utility of the BIOMONITOR to detect AF prior to an ablation procedure. Additional data of interest will be collected and assessed.

2.1.1 Primary Objective

The primary objective of this study is to determine the diagnostic utility of the BIOMONITOR to detect AF within study subjects who are being evaluated for an ablation. Specifically, the diagnostic sensitivity of the BIOMONITOR will be determined by comparing AF events detected by the BIOMONITOR and 48 hr Holter monitor for each subject. Using the 48 hr Holter monitor as the gold standard, subjects with AF events detected by the BIOMONITOR will be categorized as true positive or false positive.

It is expected that sensitivity will be greater than 90% in detecting AF within study subjects that are being evaluated for ablations.

Diagnostic Sensitivity:

H_o: The Sensitivity (Se) for detecting at least one true positive AF episode per subject will be less than or equal to 90%. ($Se \leq 90\%$)

H_a: The Sensitivity for detecting at least one true positive AF episode per subject will be greater than 90% ($Se > 90\%$)

A rejection of the null hypothesis would demonstrate that there is evidence that Sensitivity is greater than 90%.

2.1.2 Additional Data of Interest

Additional information will be collected to characterize the study population, BIOMONITOR usage, and progress of the study. Specifically, data of interest will include:

- Baseline demographics, including age, gender, height, weight, race and ethnicity (optional)
- Medical history
- Cardiovascular medication
- Insertion procedure information, including success/failure of insertion, procedure times, location and orientation of the BIOMONITOR, and reason for insertion. Data may be collected retrospectively if insertion occurred prior to enrollment.
- Inserted device information, including model, serial number, and insertion date
- Ablation procedure information, including date of ablation and the utility of the BIOMONITOR in determining ablation candidates

- Compliance to protocol requirements and study visit schedule
- Success of Home Monitoring transmissions
- BIOMONITOR performance during the study including, but not limited to, R-wave amplitude and arrhythmia detections as reported using BIOTRONIK Home Monitoring®
- AF episodes as detected by the Holter monitor and BIOMONITOR, as well as additional arrhythmic episodes. AF detections will be used to support patient, episode, and duration metrics including sensitivity, specificity, positive predictive value, and negative predictive value of the BIOMONITOR.
- Visibility of P-waves from recorded BIOMONITOR episodes
- AF episodes within the pre-Holter observation period

2.2 Subject Status Definitions

The subject status definitions utilized in this study are provided in Table 1.

Table 1: Subject Status Definitions

Subject Status	Definition
Provisionally Enrolled	Subject has provided written informed consent but has not initiated 48 hr Holter monitoring. Provisionally enrolled subjects that initiate 48 hr Holter monitoring will be considered fully enrolled. Provisionally enrolled subjects that do not initiate 48 hr Holter monitoring will be exited. These subjects will be included in the additional data of interest analysis population.
Screen Failure	Subject has signed consent, but at the time of consent it was identified the subject does not meet all inclusion/exclusion criteria OR Subject consented prior to insertion, but exited prior to insertion or does not receive a BIOMONITOR. Subject will be exited and will not be included in the analysis population.
Enrolled	Subject has met all inclusion and exclusion criteria, provided written informed consent, successfully inserted with a BIOMONITOR, and initiates 48 hr Holter monitoring. Subject will be included in the analysis population.

2.3 Study Size and Duration

During this study, data will be gathered, analyzed, and reported to evaluate the diagnostic utility of the BIOMONITOR. It is anticipated that up to 100 subjects will be enrolled to have 60 subjects who will complete 48 hr Holter monitoring and will be followed for three months post 48 hr Holter monitoring at up to 5 U.S. sites.

2.4 Sample-Size Analysis

The study is designed to limit the number of subjects involved while still exposing the device to a sufficiently large subject population to evaluate the utility of BIOMONITOR in subjects that are being evaluated for AF ablation. A sample size of 60 subjects with evaluable data sets is required to evaluate the diagnostic sensitivity with the following assumptions:

- Prevalence of AF during Holter test: 50%
- Confidence interval: 95%
- Precision level: 6.35%
- Expected patient-based sensitivity: 97%
- Drop-out rate after 48 hr Holter monitoring is initiated: 8%

To account for expected attrition due to subject withdrawal following consent but prior to completion of the study testing period:

- Up to 100 subjects will be provisionally enrolled
- Assumed 40% drop out rate between consent and the initiation of 48 hr Holter monitoring (e.g. R-wave amplitude <0.25 mV, no AF detection during pre-Holter observation period, withdrawn consent, etc.)
- Sixty subjects will undergo 48 hr Holter monitoring (fully enrolled)

2.5 Data Analyses

Descriptive statistics will be used to present and summarize the data collected in the clinical study. Frequency distributions and cross tabulations will be presented for discrete variables. Means, standard errors, and ranges will be presented for continuous variables.

2.5.1 Objective Analysis

The primary objective analysis will calculate the diagnostic sensitivity of the BIOMONITOR. Diagnostic sensitivity is the ability of the BIOMONITOR to correctly identify subjects who have AF as determined by the Holter monitor.

Specifically, diagnostic sensitivity is determined as:

$$Diagnostic\ sensitivity = \frac{Number\ of\ TP\ patients}{Number\ of\ TP + Number\ of\ FP\ patients}$$

Where TP is true positive and FP is false positive.

To test the primary hypotheses, sensitivity will be calculated and a one-tailed binomial test will be implemented to determine if there is evidence to support the rejection of the null hypothesis.

2.5.2 Analysis for Data of Interest

Additional data of interest, which includes the characterization of the insertion procedure and device functionality, will be analyzed quantitatively and statistically where appropriate. All available results will be categorized and summarized.

Data from the 48 hr Holter recording will support metrics including sensitivity, specificity, positive predictive value, and negative predictive value. Holter monitoring will be used as the gold standard for AF detection. Sensitivity is defined as the proportion of true positives that are correctly identified as positive. Specificity is defined as the proportion of true negatives that are correctly identified as negative. The positive predictive value is defined as the proportion of positive detected episodes that are true positive. The negative predictive value is defined as the proportion of negative detected episodes that are true negative. Evaluation may be performed on an episode, subject, or duration basis. Additional, non-AF episodes recorded on the BIOMONITOR may be compared to Holter data to confirm the onset of different arrhythmias.

2.5.3 Analysis Population

The analysis population for the primary objective includes all subjects that are enrolled in the study and have evaluable 48 hr Holter data and BIOMONITOR data. If an evaluable 48 hr Holter contains segments which are marked as not interpretable by the Holter Core Laboratory, these segments will be excluded from analysis. Subjects may be allowed to repeat 48 hr Holter monitoring if the Holter Core Laboratory determines a significant portion of the recording is uninterpretable.

Evaluable BIOMONITOR data is defined as successful collection of the complete BIOMONITOR data set from the 48 hr Holter period. In the event that some BIOMONITOR detections are not available due to the number of detected events exceeding the device storage capacity, the segments with missing BIOMONITOR information will be excluded from the analysis.

Data of interest elements that require comparison to the 48 hr Holter monitor data will use the same analysis population. Analysis for additional data of interest will be completed with both provisionally enrolled and fully enrolled study populations.

2.5.4 Interim Analysis

In the BIO-Precision study, one interim analysis is planned and will occur once all eligible fully enrolled subjects have completed their 48 hr Holter monitoring visits. This analysis will assess the outcomes of the primary objective. At this interim analysis, the study objectives and additional data of interest may be evaluated to characterize initial results of the BIO-Precision Study.

3. PROTOCOL REQUIREMENTS

3.1 Patient Population

The investigator is responsible for screening all potential subjects and selecting those who are appropriate for study inclusion. Potential subjects will be evaluated to determine if they meet the inclusion and exclusion criteria described below in Sections 3.1.3 and 3.1.4. The subjects selected for participation should be from the investigator's general patient population according to the inclusion and exclusion criteria. Patients who require a legally authorized representative will not be allowed in the study.

3.1.1 Indications

The BIOMONITOR is a SCRM that records subcutaneous ECG (sECG) and is indicated for:

- Patients with clinical syndromes or situations at increased risk of cardiac arrhythmias
- Patients who experience transient symptoms that may suggest a cardiac arrhythmia

The device has not been tested for and it is not intended for pediatric use.

3.1.2 Contraindications

There are no known contraindications for the insertion of the BIOMONITOR. However, the patient’s particular medical condition may dictate whether or not a subcutaneous, chronically inserted device can be tolerated.

3.1.3 Inclusion Criteria

To support the objectives of this investigation, the inclusion criteria at the time of patient enrollment for this study include the following requirements:

- Meet the indications for SCRM insertion according to local regulations
- Patient is able to understand the nature of the study and provide written informed consent
- Inserted within the prior 30 days, or scheduled for insertion within 14 days, with BIOTRONIK’s most current SCRM
- Diagnosed with paroxysmal[9] atrial fibrillation and being evaluated for an AF ablation
- Agree to wearing a 48 hr Holter monitor
- Able and willing to complete all study visits at the study site for the study duration

- Able and willing to use a CardioMessenger® and accepts Home Monitoring concept
- Age greater than or equal to 18 years

3.1.4 Exclusion Criteria

To support the objectives of this investigation, the exclusion criteria at the time of patient enrollment include the following requirements:

- Patient meets none of the indications for a BIOMONITOR
- Patient is planned to have an ablation prior to BIOMONITOR insertion or 48 hr Holter monitoring visit
- Patient is currently diagnosed with long-standing persistent[9] or permanent AF
- Patient is enrolled in another study that may change or alter the cardiac rhythm that occurs prior to the completion of the Holter
- Currently indicated for or implanted with a pacemaker, ICD device, or hemodynamic monitoring system
- Life expectancy less than 6 months
- Patients reporting pregnancy at the time of enrollment

For patients enrolled after BIOMONITOR insertion:

- R-wave sensing <0.25 mV according to the most recent Home Monitoring CardioReport or device interrogation available prior to enrollment

After the pre-Holter observation period but prior to 48 hr Holter monitoring initiation, confirm the absence of the following exclusion criteria based on the CardioReport collected at the end of the observation period:

- No AF episodes observed or transmitted during pre-Holter observation period
- R-wave sensing <0.25 mV during pre-Holter observation period as reported by the 24 hr mean or mean value since last follow-up

3.2 Study Procedures

Subjects with a previously inserted BIOMONITOR will be provisionally enrolled once consent is given and will be considered fully enrolled once 48 hr Holter monitoring has been initiated. Subjects consented prior to insertion will be considered provisionally enrolled until the successful insertion of a BIOMONITOR and the initiation of 48 hr Holter monitoring.

BIOTRONIK Home Monitoring® should be activated in all subjects. Data will be collected at all visits starting at insertion (e.g. enrollment, Home Monitoring data check following the pre-Holter observation period, 48 hr Holter monitoring initiation and completion visit, and study exit). Enrollment data will include informed consent, subject demographics, and relevant medical history.

Insertion data will include procedure time, insertion location and orientation, and device serial numbers. Following insertion or at the time of enrollment, for subjects previously inserted with a BIOMONITOR, the BIOMONITOR must be programmed to the required programming settings to initiate the pre-Holter observation period.

Following the 12 to 16 day pre-Holter observation period, the presence of AF episodes and R-wave sensing performance will be evaluated. Subjects with no AF episodes during this time will not complete the Holter visit and will be exited from the study. Subjects with R-wave sensing <0.25 mV, as reported by the 24 hour mean or the mean value since last follow-up on the Home Monitoring CardioReport collected at the end of the pre-Holter observation period, will not complete 48 hr Holter monitoring and will be exited form the study.

For subjects presenting with at least one AF episode during the pre-Holter observation period, patient specific BIOMONITOR programming settings may be provided by BIOTRONIK prior to starting 48 hr Holter monitoring. Data will be collected at the 48 hr Holter monitoring initiation visit and will include Holter start time and selected programming. Data will also be collected at the completion of 48 hr Holter monitoring including the Holter recordings and all sECGs from the BIOMONITOR. The Holter data will be sent to the Holter Core Laboratory for evaluation.

BIOMONITOR performance data will be collected throughout the course of this study by BIOTRONIK Home Monitoring®. Subjects will be followed for three months after the completion of their 48 hr Holter visit. At study exit, data will be collected on adverse events and reason for study exit. Additionally, date of ablation, if performed, and physician feedback on the diagnostic utility of the BIOMONITOR to determine the need of the ablation will be collected at the time of study exit.

Study Procedure Visits:

- Enrollment (subjects are considered provisionally enrolled until undergoing successful insertion and initiation of 48 hr Holter monitoring)
- Insertion (if subject does not have an existing BIOMONITOR)
- Home Monitoring data check (after completion of the pre-Holter observation period)
- 48 hr Holter Monitoring Initiation
- 48 hr Holter Monitoring Completion

Table 2 summarizes the study procedures. Table 3 summarizes the visit schedule.

Table 2: Study Procedures

	Enrollment	Insertion[1]	Home Monitoring data check	48 hr Holter Monitoring Initiation Visit[2]	48 hr Holter Monitoring Completion Visit	Study Exit
Informed Consent (enrollment)	X					
Demographics and Medical History	X					
Insertion Information		X				
Device Programming	X[3]	X[4]		X		
Device Evaluation and Data Collection			X	X	X	
Holter Data Collection					X	
Adverse Event Assessment		X		X	X	X[5]
Ablation Procedure Information						X
Complete eCRF	X	X	X	X	X	X

[1]Insertion should be completed within 14 days of provisional enrollment/informed consent. If subject has a prior insertion, retrospective data collection of insertion procedure information will be required.
[2]48 hr Holter Monitoring Initiation Visit should occur within 7 days following the pre-Holter observation period.
[3]Device programming is required at enrollment for subjects enrolled after BIOMONITOR insertion.
[4]Device programming is required at insertion for subject enrolled prior to BIOMONITOR insertion.
[5]Adverse event assessment at study exit will involve medical record review for reportable events and to identify updates to previously reported events.

Table 3: Study Visit Schedule

	Visit Window		
Enrollment	30 days post BIOMONITOR insertion	-OR-	14 days prior to BIOMONITOR insertion
Insertion	30 days prior to enrollment	-OR-	14 days post enrollment
Home Monitoring data check	At the completion of the 12-16 day Pre-Holter Observation Period		
48 hr Holter Monitoring Initiation Visit	Within 7 days of the Home Monitoring data check		
48 hr Holter Monitoring Completion Visit	48 hours after the Holter Monitoring Initiation Visit		
Study Exit	Three months (-0/+30 days) after the 48 hr Holter Monitoring Completion Visit		

3.2.1 Pre-Screening

Prior to consent, the patient's medical history must be reviewed in order to ensure that the patient is an appropriate candidate for the study. This review should include verification of any available historical inclusion and exclusion criteria. This includes having a BIOMONITOR inserted no more than 30 days prior to date of consent or having plans to insert a BIOMONITOR no more than 14 days after consent. Written informed consent must be obtained from the patient prior to collecting any study specific data.

3.2.2 Consent and Eligibility

If the potential subject meets all inclusion and exclusion criteria (see sections 3.1.3 and 3.1.4), the potential subject is informed about the study and asked to read and sign an Informed Consent Form. The potential subject should be provided with sufficient time to consider participation in the study. The consent process, including discussion of the study, should be documented within the subject's medical record. Consented subjects must be entered in the subject identification log and will be reflected on the electronic enrollment log once entered in the electronic data capture system.

The following data collection and reporting procedures are performed at the consent visit:

1. Verification that subject meets all of the inclusion criteria and none of the exclusion criteria

2. Obtain informed consent and upload the unredacted signed informed consent form to the Informed Consent eCRF*

3. Complete all required eCRFs

If the subject is consented after BIOMONITOR insertion, the BIOMONITOR should be programmed to the required programming settings and the pre-Holter observation period should be initiated at time of enrollment.

3.2.3 Insertion

BIOMONITOR insertion should occur no more than 14 days after informed consent (consented prior to insertion) or no more than 30 days prior to informed consent (consented after insertion). Insertion details and device information will be collected retrospectively if insertion occurred prior to consent.

The following insertion data and procedures will be collected for enrolled subjects:

1. Collect insertion information
   - Date of insertion procedure
   - Insertion location
   - Device orientation
   - Primary indication for insertion
2. Collect inserted system information model and serial number
3. Review for any reportable adverse events (See section 9.1)
   a. Only adverse events occurring in enrolled subjects on or after the date of insertion through the duration of the study will be collected.
   b. All insertion procedure-related, device-related and non-procedure non-system related AEs will be reported as outlined in Section 9.1.
4. Complete all required eCRFs and upload source documentation

* Sites that are unable to upload unredacted signed informed consents will be asked to provide a copy of the IRB and/or institutional policy stating they are not allowed to upload unredacted source documentation.

If the subject is consented prior to BIOMONITOR insertion, the BIOMONITOR should be programmed to the required programming settings at the time of insertion and the pre-Holter observation period should be initiated following insertion and programming.

3.2.4 Baseline Medical History

Baseline medical history information will be entered into the Enrollment eCRF, if available. Baseline information includes, but is not limited to demographics, arrhythmias, comorbidities and cardiovascular medication. Reported data should be from the medical record and obtained from records no more than 90 days prior to consent. If subject is a screen failure, baseline medical history will not be collected for the study.

3.2.5 Pre-Holter Observation Period

Subjects will undergo a 12 to 16 day pre-Holter observation period following enrollment, for subjects inserted with a BIOMONITOR prior to consent, or following insertion, for subjects consented prior to BIOMONITOR insertion. The BIOMONITOR must be programmed to the required programming settings either at enrollment or insertion, respectively. Subjects with a new BIOMONITOR device should be educated on the set up and use of the CardioMessenger to ensure Home Monitoring data is transmitted during the 12 to 16 day observation period. For subjects implanted before consent, Home Monitoring transmission status should be verified and any transmission issues resolved.

Following this pre-Holter observation period, a Home Monitoring data check will be performed and CardioReport obtained, containing a listing of all episode recordings. Information on AF episodes within the observation period will be collected. 48 hr Holter monitoring will not be performed for subjects with no AF episodes recorded or transmitted during the observation period or in subjects with R-wave sensing < 0.25 mV, as reported on the CardioReport collected at the completion of the observation period, and these subjects will exit the study. For subjects with AF episodes, BIOTRONIK may provide additional programming settings prior to initiation of 48 hr Holter monitoring.

3.2.6 48 hr Holter Monitoring Initiation Visit

Subjects should undergo 48 hr Holter monitoring within 7 days of the completion of the pre-Holter observation period. The following study procedures are performed at the 48 hr Holter Monitoring Initiation visit:

1. Ensure Holter monitor and BIOMONITOR date and time are accurate and synchronized.
    a. Ensure correct time and date on the programmer, which will set the time on the BIOMONITOR upon interrogation.
    b. Adjust Holter time and date to match the BIOMONITOR.

2. Interrogate the BIOMONITOR and clear previous stored episodes and reset device counters.
    a. Navigate to the 'Recordings' page of the BIOMONITOR from the main follow up screen.
    b. From the 'Recordings' page, select 'Restart'
    c. Navigate to the 'Diagnostics' page of the BIOMONITOR from the main follow up screen.
    d. From the 'Diagnostics' page, select 'Start statistics'
3. Reprogram the BIOMONITOR to updated programming settings based on the data collected from the pre-Holter observation period, if applicable. Updated programming will be provided by BIOTRONIK prior to the 48 hr Holter initiation visit.
4. Provide the subject with the Holter Monitor and program the Holter Monitor for 48 hours of monitoring.
    a. Educate the subject on proper Holter use for the next 48 hours.
    b. Schedule the subject to return following 48 hours of Holter monitoring.
5. Review for any new reportable adverse events and updates to previously reported adverse events.
6. Review and complete the appropriate eCRFs, including upload of BIOMONITOR interrogation, including current programming, and documentation of 48 hr Holter Monitoring Initiation visit to EDC.

3.2.7 48 hr Holter Monitoring Completion Visit

Subjects should undergo the Holter Monitoring Completion visit 48 hours after the Holter Monitoring Initiation visit. The following study procedures are performed at the Holter Monitoring Completion visit:

1. Verify Holter monitor and BIOMONITOR date and time are accurate and synchronized.
    a. Record standard time, Holter monitor time, and BIOMONITOR time to document any differences in the dates/times.
2. At the end of the 48 hours, collect Holter device and obtain the Holter data.
3. Interrogate the BIOMONITOR and download all recorded episodes and the episode list.
    a. Navigate to the 'Recordings' page of the BIOMONITOR from the main follow up screen.
    b. From the 'Recordings' page, view all recordings.
    c. Ensure data, including the recording list, is saved on a USB for upload to EDC.

4. Program BIOMONITOR parameters to best suit the needs of the subject, per physician discretion.
5. Review for any new reportable adverse events and updates to previously reported adverse events.
6. Send Holter data to the Holter Core Laboratory with required Holter Core Laboratory documentation.
7. Review and complete the appropriate eCRFs, including upload of BIOMONITOR data and documentation of 48 hr Holter Monitoring Completion visit in EDC.

If the Holter Core Laboratory determines a significant amount of the Holter recording is uninterpretable, the site will be notified and the subject may be asked to complete a second 48 hr Holter monitoring session if they are willing and able, and ablation has not been completed or is not scheduled to be complete prior to completion of the repeat Holter. If a repeat Holter is completed, the 3 month follow-up after Holter completion will be based off of the date of completion of the first 48 hr Holter monitoring session.

3.2.8 System Revisions

Subjects who have a revision of the BIOMONITOR after successful insertion of the device will be exited. The reason and date of exit will be obtained and a Study Exit eCRF will be completed.

3.3 Study Exits

Regular study exit will occur 3 months (-0/+30 days) after 48 hr Holter monitor completion. Occurrence of ablation procedure will be documented in the Study Exit eCRF.

Once a subject is enrolled and successfully undergoes insertion, every effort should be made to continue to follow the subject in the study. However, it is inevitable that some subjects will decline to participate further, change geographic location, or become non-compliant with the visit schedule. Appropriate source documentation must be uploaded to the Study Exit eCRF. For all subjects that have a Holter recording initiated and are fully enrolled, data collected through the date of exit may be used for analysis. If the BIOMONITOR is explanted, the subject will be withdrawn.

The following study procedures are performed at Study Exit:

1. Review the subject's medical records to ensure that all protocol defined adverse events have been documented in the EDC system. This includes any new reportable adverse events and updates to previously reported adverse events.
    a. All previously unreported, protocol defined adverse events should be documented on Adverse Event eCRFs.
2. Determine the reason for study exit.

3. Review and complete the appropriate eCRFs.
4. Appropriate source documentation must be uploaded to the Study Exit eCRF.

For fully enrolled subjects, the following study procedures are also performed at Study Exit:

1. Collect date of ablation procedure, if performed, and information on BIOMONITOR utility to make treatment decisions regarding whether or not to perform an ablation.

3.3.1 Screen Failures

Screen failures, as defined in Section 2.2, will be exited in the EDC system. Subjects with unsuccessful insertion procedures are considered screen failures. The reason and date of withdrawal will be obtained and a Study Exit eCRF will be completed.

3.3.2 Withdrawal of Consent

If consent is withdrawn, the reason and date of withdrawal will be obtained and a Study Exit eCRF will be completed.

3.3.3 Subject Death

In the event of subject death during study participation, personnel at the study site are asked to notify BIOTRONIK as soon as possible by completing a Study Exit eCRF. If subject death was associated with an adverse event, an Adverse Event eCRF will also be required.

The following information should be provided for any subject death:

- Subject records such as a death certificate, death report source documentation worksheet signed by the investigator, or other relevant medical records that include the following details:
  - Date of death
  - Place death occurred
  - Immediate cause of death

Whenever possible, devices that are removed should be returned to BIOTRONIK for analysis.

3.3.4 BIOMONITOR Removal

Any subject who has the BIOMONITOR removed during the follow-up period will be withdrawn from the study. Study Exit eCRF should only be completed after documentation of the device removal or replacement procedure is available (see Section 3.2.8).

Whenever possible, devices that are removed should be returned to BIOTRONIK for analysis.

3.3.5 Lost to Follow-up

Subjects lost to follow-up are those for whom contact is lost despite the investigator's best efforts to locate the subject. Study sites should attempt to contact these subjects in order to maintain study visit compliance and all contact attempts should be documented. At a minimum, the site should make and document two attempts to contact the subject by phone and one attempt by certified mail.

In the event the subject cannot be contacted using the above methods, the subject should be exited from the study by completing a Study Exit eCRF. BIOTRONIK Home Monitoring® device data may be utilized to support analysis of additional data of interest in the event that the subject is lost to follow-up.

3.3.6 Investigator Initiated Withdrawal

In addition to subject initiated withdrawal of consent, a study site investigator may determine that a subject should be withdrawn for other reasons such as following with a different physician, changes to insurance, non-compliance, etc. Details related to investigator initiated withdrawal such as reason for withdrawal and attempts made to retain subject should be collected. The investigator determined end date of subject participation should be reported as the date of exit.

3.3.7 Pre-Holter Observation Period Withdrawal

Subjects will be withdrawn from the study if there are no recorded or transmitted AF episodes during the pre-Holter observation period. Additionally, if R-wave sensing is <0.25 mV as reported by the 24 hr mean or mean value since last follow-up on the CardioReport obtained at the end of the observation period. The reason and date of withdrawal will be obtained and a Study Exit eCRF will be completed.

3.3.8 Study Participation Complete

All subjects who undergo successful insertion procedures are expected to be followed for three months post 48 hr Holter monitoring. After a subject completes three months of Home Monitoring post 48 hr Holter, their study participation is complete and the subject will be exited from the study by completing a Study Exit eCRF.

4. DATA COLLECTION

4.1 IRB Approval

Institutional Review Board (IRB) approval is required from each institution prior to participation in this clinical study. Subject enrollment may not begin until both the

IRB and BIOTRONIK have granted approval for the study site. IRB approval is also required throughout the duration of this clinical study. If IRB approval is withdrawn, BIOTRONIK must be notified within 5 working days.

4.2 Other Institutions and Physicians

This clinical study is not transferable to other institutions attended by the study site investigators unless prior approval is obtained from both BIOTRONIK and the appropriate IRB. Only approved investigators are authorized to participate in the study. If a site enrolls subjects after insertion, the inserting physician does not need to be an approved investigator.

There are certain situations where a study site investigator might not be immediately available to provide the necessary medical care for a subject enrolled in the clinical study (such as a subject emergency room visit for medical treatment). In these instances a protocol non-compliance will not be issued and all available data will be utilized. In any such situations, the IRB and the investigator must continue to provide oversight for that patient's medical care and rights as a research subject.

4.3 Informed Consent

All subjects must sign and date an IRB approved Informed Consent Form (ICF) prior to collecting any study specific data. Informed consent should be obtained in accordance with the FDA regulations (21 CFR Part 50) and any other national or local requirements. The study site is required to inform BIOTRONIK and the reviewing IRB within 5 days if any subject was not appropriately consented to participate in the study.

4.4 Data Collection

4.4.1 Electronic Data Capture (EDC)

MedNet Solutions Incorporated is a privately held company that specializes in web-based clinical data management technology. MedNet will host the EDC system and provide a secure environment that is accessible to authorized individuals through the internet. BIOTRONIK will implement a study specific configuration using this software to meet the data collection requirements of the protocol. The EDC system is 21 CFR Part 11 compliant and is the platform for electronic case report form (eCRF) data entry; clinical data discrepancy resolution; and provides access to reports for BIOTRONIK, specified study sites, and any other parties authorized by BIOTRONIK.

4.4.2 Electronic Case Report Forms (eCRFs)

Original data will be collected from each study site and recorded into the EDC system via completion of eCRFs, which are audited and monitored by BIOTRONIK.

The study site investigators will be required to use an electronic signature to approve the content of the data reported in the eCRFs.

4.4.3 BIOTRONIK Home Monitoring® Data

Home Monitoring Service Center data from enrolled study subjects will be accessible to the sponsor from insertion through the date of subject withdrawal of consent, subject death, or completion of the study. For subjects that are exited for other reasons (including physician withdrawal, subject moving, and lost to follow-up) BIOTRONIK Home Monitoring® data may be collected for the proposed study duration (i.e., up to 3 months post-ablation). BIOTRONIK Home Monitoring® data might be used for evaluation and publication if desired by the sponsor.

All data are transferred to the sponsor in a pseudonymized form. Data includes all information transmitted from the device (e.g. sECGs, statistics).

4.5 Data Quality Control

BIOTRONIK will review study data reported in the EDC system. At any time, reports may be generated on data completion and missing data for each study site. The EDC system will be used to track received and expected follow-up data and eCRFs for each participant. This system provides the capability to monitor the status, volume, and disposition of data. In addition, study data will undergo automatic edit and plausibility checks, which provides information to the study sites to help improve and maintain data quality control procedures designed to detect inaccuracies and inconsistencies.

To ensure protocol compliance at all participating investigational sites, BIOTRONIK monitors will conduct centralized monitoring and/or monitoring visits throughout the course of the study (see section 9 for more information).

To ensure compliance with federal regulations, internal policies and procedures, and the study protocol, Holter Core Laboratories and EDC vendor will also be monitored and/or audited by BIOTRONIK or a BIOTRONIK representative during the course of the study.

4.6 Subject Data Confidentiality

All information and data collected for BIO-Precision concerning subjects or their participation in this investigation will be considered confidential by BIOTRONIK, BIOTRONIK's parent company, subsidiaries, and affiliates, as well as contracted designees, Holter Core Laboratory, EDC vendors, and any other authorized third parties.

Applicable national and local laws pertaining to subject data protection will be applied to the study. As such, all data used in the analysis and reporting of this investigation will not include an identifiable reference to specific subject name, or

other protected confidential subject, nor will it contain other confidential subject identifiers.

In order to verify the study data and ensure study integrity, monitors and representatives from BIOTRONIK, the U.S. FDA, other national regulatory and/or public health authorities and the reviewing Investigational Review Board may review and/or copy the study records. Source documents used to support Holter Core Laboratory activities will have confidential subject identifiers and other protected health information redacted prior to transmission.

4.7 Protocol Non-compliance

Study site investigators are required to conduct this study in accordance with the signed investigator agreement and clinical protocol. The investigator shall notify BIOTRONIK and the reviewing IRB in writing no later than 5 working days after any significant deviation from the clinical protocol to protect the life or physical well-being of a subject in an emergency. Except in such emergency, prior approval by BIOTRONIK is required for significant deviations from the clinical protocol.

The site is responsible for reporting non-compliance via Protocol Non-compliance eCRFs. BIOTRONIK categorizes protocol non-compliance instances as either violations or deviations.

4.7.1 Protocol Violations

Protocol violations are defined as instances where the protocol requirements and/or regulatory guidelines were not followed, and are generally more serious in nature. Protocol violations are considered to potentially affect the scientific soundness of the plan and/or the rights, safety, or welfare of subjects.

Protocol violations include, but are not limited to:

- Failure to obtain consent or other instances in which the subject did not provide consent
- Subject enrolled, but did not meet all inclusion/exclusion criteria

4.7.2 Protocol Deviations

Protocol deviations are defined as instances where protocol requirements and/or regulatory guidelines were not followed, and are generally less serious in nature than violations. Protocol deviations generally do not affect the subject's rights, safety, or well-being and/or the completeness, accuracy, and reliability of data supporting the primary objective. Instances of non-compliance should be considered a deviation if it does not meet the criteria for being considered a violation.

Protocol deviations include, but are not limited to:

- Informed Consent documentation issues such as incomplete ICF, missing dates for signature(s), missing initials or illegible information, subject signature date completed by someone other than subject, utilization of an outdated or non-IRB approved ICF, or incomplete associated forms required at time of consent, etc. (this is not an exclusive list)
- Visit not performed within the visit window
- Device information or other required data not obtained at follow-up visit

4.7.3 IRB Reporting of Non-Compliance

The study site must notify the reviewing IRB of all non-compliance issues per the IRB and protocol reporting requirements. At a minimum, all violations and non-compliance issues related to informed consent and informed consent documentation should be reported to the IRB.

In some instances, such as failure to obtain consent, the study site should also seek guidance from the IRB to ensure the subject received appropriate information to consider her or his participation in the study.

The site should provide a copy of the IRB protocol non-compliance notification (as applicable) to BIOTRONIK.

5. RISKS AND RISK MINIMALIZATION

All devices, device programmers, and Home Monitoring® systems included in the BIO-Precision Study are legally marketed and being prescribed by physicians according to FDA approved indications for use. Additionally, all visits, outside of the 48 hr Holter monitoring visit, in this post-market observational study are standard of care. There are no new known risks associated with participation in this study. Please refer to the product manuals for risks associated with the BIOMONITOR.

According to the American Heart Association, wearing a Holter monitor poses no risks other than the possibility of mild skin irritation due to the tape or adhesives associated with the electrodes.

The only research related risk is the potential loss of confidentiality that is minimized as outlined in Section 4.6.

6. STUDY ORGANIZATION

6.1 Sponsor

BIOTRONIK is the "sponsor" of the clinical investigation. A "sponsor" is defined as an entity that initiates but does not conduct an investigation. BIOTRONIK's responsibility as the clinical study sponsor is to ensure protocol and regulatory compliance through proper monitoring of the investigation.

6.2 Holter Core Laboratory

The Holter Core Laboratory will be responsible for manually annotating arrhythmia episode onset and termination from the Holter monitor, classification of these episodes, and reporting in the EDC system. The Core Lab will create a study specific charter defining the Holter monitor data review and annotation process, specifically detailing review guidelines along with appropriate response timelines.

7. MONITORING

7.1 Summary

The responsibility of BIOTRONIK as sponsor is to ensure protocol and regulatory compliance through proper monitoring of the clinical study at sites. As a study site investigator, the physician is responsible for conducting the clinical study in accordance with the signed Investigator Agreement, the study protocol, applicable laws, and FDA and/or local regulations and any conditions of approval imposed by the reviewing IRB. The study site principal investigator must also accept responsibility for all aspects of the clinical study including the actions of any sub-investigators participating in the clinical study at the investigational site.

BIOTRONIK utilizes a risk-based monitoring strategy consistent with FDA's Guidance for Industry: Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring, August 2013[11]. Risk-based monitoring starts with performing a study risk assessment of the identified critical data and processes. The resulting monitoring plan focuses on targeted source data verification and trend analyses to improve oversight and data quality, while integrating predefined triggers for additional on-site monitoring. The detailed study risk-based monitoring plan developed by BIOTRONIK focuses on a combination of centralized and on-site monitoring. Monitors may periodically conduct on-site or remote monitoring visits periodically during the clinical study in accordance with the monitoring plan. On-site monitoring visits are an in-person evaluation carried out at the study site. Remote monitoring visits are a remote evaluation of a study site for those sites providing remote sponsor access to the electronic medical record system. Sites are required to support these monitoring visits and the study monitoring effort, including either direct monitor or site-assisted access to the applicable medical record systems. The study site principal investigator is encouraged to be available during monitoring

visits. Monitoring visits will also provide an assessment of the continued acceptability of the facilities to continue participation in the study.

Centralized monitoring is conducted via electronic case report forms (eCRFs) through the source data verification of source documents uploaded to the eCRF. Some examples of data that may be monitored remotely include: unredacted informed consent forms, eligibility, baseline data, insertion, study exit, device data, and adverse events reported in the EDC system. Sites are required to support centralized monitoring by providing signed, dated, final source documents to BIOTRONIK in order to source data verify data reported in the EDC system and resolving queries in a timely manner.

The E6(R2) Good Clinical Practice: Integrated Addendum to International Council for Harmonisation (ICH) E6 (R1) Guidance for Industry dated March 2018 outlines the ALCOA-C guidelines for source documentation. All source documentation and study records should meet these ALCOA-C guidelines of attributable, legible, contemporaneous, original, accurate and complete. This guidance ensures the confidentiality, credibility, accuracy and validation of research records. All pages of source documents should be labelled with the subject ID. It is critical that the fully executed and unredacted informed consent form and all necessary source documentation are uploaded to the EDC in a timely manner.

The entries in the eCRF will be reviewed and source data verified by monitors (authorized BIOTRONIK personnel, or by authorized BIOTRONIK designees) to ensure that the study site investigators and the study team conducts the study in accordance with the protocol and applicable FDA and local laws and regulations to ensure adequate protection of the rights, safety and wellbeing of subjects and the quality and integrity of the resulting data. In addition, BIOTRONIK may require the presence of personnel from BIOTRONIK at the insertion and/or follow-up visits outlined in this protocol in order to assist the study site investigators and other site personnel.

Through monitoring, BIOTRONIK will assess the site’s performance in the following areas:

- Verification that informed consent was obtained and documented properly
- Adherence to protocol eligibility criteria and requirements
- Conduct and documentation of procedures and assessments related to:
    - Study objectives
    - Protocol required data collection and procedures
    - Evaluating, documenting, and reporting adverse events, and withdrawals, especially when a withdrawal may be related to an adverse event
    - Investigator oversight and delegation of authority to site personnel
    - Verification of study-specific required documentation

- Conduct and documentation of procedures essential to trial integrity
- Adherence to applicable requirements regarding the obligations of the investigator and maintenance of records.

If a monitor becomes aware that an investigator is not complying with the signed Investigator Agreement, the study protocol, applicable laws, and FDA and/or local regulations and any conditions of approval imposed by the reviewing IRB, the monitor is obliged to notify BIOTRONIK study management. BIOTRONIK will evaluate the noncompliance and issue corrective actions, as necessary, which may include but are not limited to, re-training, discontinuing enrollment at the study site, or closing the study site.

7.2 Monitors

Monitors are trained, qualified, and designated by BIOTRONIK management to oversee the progress of an investigation at the clinical site. Additional monitors may be appointed as necessary.

8. STUDY COMPLETION

BIOTRONIK will notify the study site upon completion or termination of the clinical study or of the study site investigator's participation in the study. Whenever possible, BIOTRONIK will provide a final report and a copy of the site's eCRFs to each study site. BIOTRONIK will determine if sites will have a close out visit and provide details on closure activities to all study site investigators to ensure the investigators understand any applicable regulatory requirements, including those related to record retention. All participating study site investigators are requested to promptly notify BIOTRONIK if their financial disclosure information has any relevant changes during the course of the investigation and for 1 year following completion of the study.

9. ADVERSE EVENTS

An AE is defined as any unfavorable and unintended event that occurs during the course of the study. The investigator will be required to assess and classify the type of each reported adverse event as insertion procedure-related, device-related, non-procedure non-system related, or study procedure related. For all consented subjects, only adverse events occurring on or after the date of insertion through the duration of the study will be collected. The study site should report each adverse event via an Adverse Event eCRF and provide a copy of the IRB adverse event notification to BIOTRONIK.

9.1 Reportable Adverse Events

All insertion procedure-related, device-related, non-procedure non-system related, and study procedure related AEs will be reported. The following AEs categories, sorted by type, will be reported. The types listed below are general classifications for site reporting purposes.

9.1.1 Insertion Procedure-Related Adverse Events

The AE type will be classified as procedure-related if any one of the following occurs as a result of the insertion procedure:

- Device damage
- Excessive bleeding
- Fluid accumulation within the device pocket
- Hematoma
- Inability to insert BIOMONITOR
- Non-healing pocket dehiscence requiring intervention
- Pocket pain
- Primary infection
- Superficial infection
- Surrounding tissue damage

9.1.2 Device-Related Adverse Events

The AE type will be classified as device-related if any one of the following occurs:

- Device failure
- Device migration
- Device protrusion
- Device rejection phenomena
- Skin erosion

9.1.3 Non-Procedure Non-System Related Adverse Events

The AE type will be classified as non-procedure non-system related if any of the following occur and require device removal:

- Secondary infection
- Other non-elective intervention

9.1.4 Study Procedure Related

The AE type will be classified as study procedure related if any of the following occur as a result of Holter monitoring:

- Skin irritation at the site of electrode placement
- Other events that the investigator classifies as related to Holter monitoring

9.2 Adverse Event Reporting

BIOTRONIK requires that the investigator reports protocol-defined AEs (as defined in section 9.1) that occur during the BIO-Precision Study to BIOTRONIK. The AEs that an IRB considers reportable are dependent on the particular IRB. Investigators should follow their IRB requirements regarding AE reporting.

The study site will report the AE on the Adverse Event eCRF. Additionally, study sites may report AEs through MedWatch, FDA's adverse event reporting tool for market-released devices. As defined in BIOTRONIK's internal procedures, AEs may be reported by BIOTRONIK through manufacturer's MedWatch reports.

10. RECORDS AND REPORTS

10.3 Investigator Records

Study site investigators are required to maintain on file the following accurate, complete and current records relating to this investigation:

- All correspondence relating to the study with another investigator, an IRB, BIOTRONIK, a monitor, or the FDA (e.g., a letter sent from the investigator to the IRB)
- A copy of the clinical study protocol
- Signed investigator or research agreement
- Signed Financial Disclosure Form
- A copy of the IRB approval for the research study
- A copy of the IRB approved subject Informed Consent Form
- All clinical forms and documentation, including:
    - A copy of all signed Informed Consent Forms
    - All supporting documentation for data entered into the EDC system
    - Records of any adverse events, including supporting documentation
    - Records pertaining to subject deaths during the study

- Documentation and rationale for any deviations from the clinical protocol
- Documentation of training
- Any other records required by BIOTRONIK

Study site investigators must retain records related to the study for a minimum period of 2 years after the investigation is completed consistent with FDA regulations, IRB requirements, and institutional policies. During the required 2 year period, investigators are responsible for notifying BIOTRONIK of the following: transfer of study records, investigator site address changes, or changes in study site principal investigator status.

10.4 Investigator Reporting Responsibilities

Study site investigators are required to prepare and submit to BIOTRONIK the following complete, accurate, and timely reports on this investigation as identified in the table below which outlines the responsibilities, including time constraints, for submitted required reports. Additionally, investigators are required to provide any other information upon request from an IRB, FDA, or BIOTRONIK.

Table 4: Investigator Reporting Responsibilities

Type of Report	Prepared by Investigator for:	Time Constraints of Notification
Subject death during study participation	BIOTRONIK, IRB Documentation via EDC eCRF	BIOTRONIK as soon as possible and as required by reviewing IRB
Withdrawal of IRB approval	BIOTRONIK	Within 5 working days of receipt of notice of withdrawal of approval
Significant deviations from protocol	BIOTRONIK, IRB	Within 5 working days after emergency to protect life or physical well-being of subject, otherwise prior approval by BIOTRONIK is required
Informed consent not obtained	BIOTRONIK, IRB	Within 5 working days of occurrence
Progress Report(s)	BIOTRONIK, IRB	Submitted no less than yearly

Final report	BIOTRONIK, IRB	Within 3 months after termination or completion of the study or investigator's part of the study

10.5 Sponsor Records

BIOTRONIK will maintain the following records:

- All correspondence with the investigator(s), IRB, and FDA that pertains to the study
- Investigator agreements, financial disclosures, and current curriculum vitae
- Name and address of each study site investigator and each IRB that is involved with the investigation
- Adverse events
- Adverse device effects
- Electronic Case Report Form data
- Confirmation of completed subject Informed Consent Forms
- Clinical study protocol
- Screening visit reports
- Monitoring visit reports
- Clinical progress reports

10.6 Sponsor Reporting Requirements

BIOTRONIK is responsible for preparing the following reports, when necessary:

Table 5: Sponsor Reporting Requirements

Type of Report	Prepared by BIOTRONIK for:	Time Constraints of Notification
Withdrawal of IRB approval	All reviewing IRBs and participating investigators	Within 5 working days after receipt of notice of withdrawal of approval
Progress report	All reviewing IRBs	Submitted at least annually
Recall and device disposition	All reviewing IRBs	Within 30 working days and will include reasons for any request that an investigator return, repair or otherwise dispose of any devices

Final report	All reviewing IRBs and participating investigators	A final report will be submitted within 6 months after completion or termination of the study.

11. REFERENCES

1. Purerfellner, H. *et al.* Miniaturized Reveal LINQ insertable cardiac monitoring system: First-in-human experience. *Hear. Rhythm* **12,** 1113–1119 (2015).

2. Mittal, S. *et al.* Safety Profile of a Miniaturized Insertable Cardiac Monitor: Results from Two Prospective Trials. *Pacing Clin. Electrophysiol.* **38,** 1464–1469 (2015).

3. Pachulski, R., Cockrell, J., Solomon, H., Yang, F. & Rogers, J. Implant evaluation of an insertable cardiac monitor outside the electrophysiology lab setting. *PLoS One* **8,** e71544–e71544 (2013).

4. Morillo, C. A., Banerjee, A., Perel, P., Wood, D. & Jouven, X. Atrial fibrillation: the current epidemic. *J. Geriatr. Cardiol.* **14,** 195–203 (2017).

5. Chugh, S. S. *et al.* Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation* **129,** 837–847 (2014).

6. Stewart, S., Hart, C. L., Hole, D. J. & McMurray, J. J. V. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. *Am. J. Med.* **113,** 359–364 (2002).

7. Ogawa, H. *et al.* Progression From Paroxysmal to Sustained Atrial Fibrillation Is Associated With Increased Adverse Events. *Stroke* **49,** 2301–2308 (2018).

8. Botto, G. L. *et al.* Presence and duration of atrial fibrillation detected by continuous monitoring: crucial implications for the risk of thromboembolic events. *J. Cardiovasc. Electrophysiol.* **20,** 241–248 (2009).

9. Calkins, H. *et al.* 2012 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design. *J. Interv. Card. Electrophysiol.* **33,** 171–257 (2012).

10. Ciconte, G. *et al.* Atrial fibrillation detection using a novel three-vector cardiac implantable monitor: the atrial fibrillation detect study. *Eur. Eur. pacing, arrhythmias, Card. Electrophysiol. J. Work. groups Card. pacing, arrhythmias, Card. Cell. Electrophysiol. Eur. Soc. Cardiol.* **19,** 1101–1108 (2017).

11. *Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring, Guidance for Industry*. (2013).

12. APPENDIX A: DEFINITION OF TERMS

CFR – Code of Federal Regulations

Device Damage – Visible damage to the antenna or device body or mechanical malfunction that leads to the inability of the device to correctly sense the heart signals.

Device Failure – Inability of the device to correctly sense the heart signals, not attributable to a mechanical malfunction that remains unresolved despite reprogramming and/or repositioning.

Device Migration – Visual, radiographic, electrical or electrocardiographic evidence of device displacement from the original implant site or electrode displacement that adversely affects device performance or subject health.

Device Protrusion – Device or antenna perforation through the skin that is not a result of skin erosion.

Device Rejection Phenomena – Reaction to device materials; includes local tissue reaction and metal sensitivity.

Excessive Bleeding – Bleeding during the insertion procedure that cannot be stopped by applying pressure alone.

Fluid Accumulation within the Device Pocket - Fluid swelling within the insertion site that is not related to infection or considered to be a hematoma, which requires surgical intervention to resolve.

Hematoma – An accumulation or persistent swelling of blood that requires evacuation, drainage, post-insertion hospitalization, or blood transfusion.

Holter Monitor – A battery-operated portable device that measures and records your heart's activity (ECG) continuously for 24 to 48 hours

Inability to insert BIOMONITOR – BIOMONITOR insertion was attempted but not successfully placed.

Long-standing Persistent AF – Long-standing persistent AF is defined as continuous AF of greater than 12 months' duration.

Non-healing Pocket Dehiscence – Separation of wound edges around the insertion site of the device that has not healed; excludes hematoma, seroma, infection, and erosion.

Paroxysmal AF – Paroxysmal AF is defined as AF that terminates spontaneously or with intervention within 7 days of onset.

Permanent AF – Permanent AF is defined as the presence of AF that is accepted by the patient and physician, and for which no further attempts to restore or maintain sinus rhythm will be undertaken. The term permanent AF represents a therapeutic attitude on the part of the patient and physician rather than an inherent pathophysiological attribute of AF.

Pocket Pain – Pain greater than 1 week post-insertion requiring intervention with a narcotic (if narcotics are not already prescribed) or requiring pocket revision.

Primary Infection – Infection requiring intervention such as IV antibiotics, device removal, or hospitalization. Excludes superficial infection that is resolved with outpatient antibiotics.

Secondary Infection – Infection that is determined not to be a result of the insertion procedure, but may be due to previous course of therapy or pre-existing infection.

Skin Erosion – Deterioration of tissue over the implant site or the movement of the device or antenna through the skin.

Superficial Infection – Infection that only involves the skin and surrounding subcutaneous tissue around the incision site of the insertion procedure that is treated on an outpatient basis or a stitch abscess that requires outpatient antibiotics.

Surrounding Tissue Damage – Significant physical damage to the pocket or surrounding subcutaneous tissues as a result of insertion procedure.