Clinical Protocol for the BioInsight Study

BioMonitor 2 In-Office Setting Insertion Safety and Feasibility Evaluation with Device Functionality Assessment

April 11, 2016

BIOTRONIK, Inc.
6024 Jean Road, Lake Oswego, Oregon 97035

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PROTOCOL SIGNATURE PAGE

The signature below constitutes the receipt and review of the BioInsight 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 US federal regulations, ICH and GCP guidelines.

PRINCIPAL INVESTIGATOR:

Signed:

_____
Name (please print)

_____ _____
Signature Date

Title:	BioInsight Study
Design:	Multi-center, prospective, non-randomized, post-market study
Purpose:	The purpose of this study is to evaluate the safety and feasibility of performing the BioMonitor 2 insertion procedure in an office setting. The study will provide data to characterize insertion procedure-related adverse events, time and resources utilized at insertion, and device functionality post-insertion. In addition, the study may provide data to support an application to CMS and private insurance for reimbursement of in-office implants of this device.
Subject Population:	Subjects indicated for continuous arrhythmia monitoring who are willing to undergo the insertion procedure in an office setting.
Enrollment:	This study will enroll up to 75 subjects.
Clinical Sites:	Up to 7 centers within the United States.
Primary Objectives:	Characterization of all insertion procedure-related adverse events within 90 days post-insertion that require additional invasive intervention to resolve.
Secondary Objectives:	• Characterization of all insertion procedure-related adverse events. • Characterization of the insertion procedure. • Characterization of device functionality post-insertion.
Clinical Events Committee Chair:	Marye Gleva, M.D., F.A.C.C, F.H.R.S. Associate Professor of Medicine Department of Cardiology Washington University School of Medicine, St. Louis, MO
Sponsor:	BIOTRONIK, Inc. Clinical Studies Department 6024 SW Jean Road Lake Oswego, Oregon 97035

1. INTRODUCTION

1.1 NAME OF DEVICE

This study is designed to investigate the BioMonitor 2, BIOTRONIK's second generation of insertable cardiac monitor (ICM). The BioMonitor 2 is available in one model, the BioMonitor 2-AF.

1.2 STUDY OVERVIEW

The purpose of this study is to evaluate the safety and feasibility of performing the BioMonitor 2 insertion procedure in an office setting. Data will be collected from up to 75 subjects from insertion through 90-days of follow-up post-insertion.

Subjects will be consented within 30 days prior to the insertion procedure and will be screened to ensure they meet all of the inclusion and none of the exclusion criteria. Subjects with successful insertions will be required to complete an initial wound check visit 7 days (window -2, +7 days) after the procedure and a routine follow-up visit at 90 days (window -15, +30 days) post-insertion.

The rate of insertion procedure-related adverse events (AEs) within 90 days post-insertion that require additional invasive intervention to resolve will be assessed. Data will also be collected on the safety and feasibility of in-office insertion procedures.

Additionally, device orientation and insertion techniques, time and resources utilized, and device functionality post-insertion will be characterized.

1.3 BACKGROUND

Based on the first generation of BIOTRONIK's ICM, the BioMonitor 2 utilizes well-established arrhythmia detection algorithms within smaller hardware. Equipped with BIOTRONIK Home Monitoring®, the BioMonitor 2 supports daily transmissions of device diagnostics and subcutaneous ECG (sECG) recordings, automatically and through patient triggers. The BioMonitor 2, cleared April 11, 2016 (K152995 number), is the successor of the BioMonitor with AF detection, cleared March 19, 2015 (K143503).

1.3.1 Rationale

ICMs and implantable loop recorders (IRLs) are subcutaneous devices capable of long-term cardiac rhythm monitoring that are useful in correlating arrhythmias with patient symptoms. Most commonly, ICMs are implanted to assist in the diagnosis of unexplained palpitations and syncope with more reliable and accurate monitoring than traditional 12-channel ECGs. ICMs are also used in the detection and management of atrial fibrillation (AF) for patients who are at high thromboembolic risk. ICMs, including BIOTRONIK's first generation BioMonitor, were originally designed after pacemaker technology. Current ICMs have significantly decreased profiles, allowing for less-invasive insertion procedures[1] and low complication rates[2-3] compared to that of pacemakers and implantable cardioverter defibrillators (ICDs).[4-5]

In recent years, many minor surgical procedures have moved from traditional hospital settings to physician office settings. While performing these procedures outside of a hospital environment presents possible additional risks to the patient, the procedures are generally lower in cost and utilize fewer resources.[6] With increased interest in performing procedures on an out-patient basis, few studies explore the safety of procedures outside of specialized clinics. Before new procedures can be adopted in an office setting, the procedure complexity, capabilities of the new location, and access to supplies, must be considered.

Unlike other cardiac devices, ICMs do not require vascular access. The low associated complication rates and simplistic insertion procedures make ICMs ideal candidates for in-office device placement. This study explores the safety of the BioMonitor 2 insertion procedure in an office setting. The study will provide data to characterize insertion procedure-related adverse events, time and resources utilized during insertion, and device functionality post-insertion. In addition, the study may provide data to support an application to CMS and private insurance for reimbursement of in-office implants of this device.

1.3.2 BioMonitor Master Study

The BioMonitor Master Study was conducted to support regulatory approvals of BIOTRONIK's first generation of ICM and is registered on ClincalTrials.gov NCT01725568. The objective of this post-market follow-up study was to confirm the safety and efficacy of the BioMonitor. There were 152 subjects implanted between October 2012 and October 2014 and observed over the course of one year. During the study, no serious complications or adverse events related to the BioMonitor were reported, and overall performance of BioMonitor was within the expected range.

1.3.3 BioMonitor Single-center AF Detect Study

BIOTRONIK conducted an AF Detection clinical study in order to assess the performance of the BioMonitor's AF feature in clinical practice. The ability of BioMonitor to detect episodes of AF was quantified in comparison with the gold-standard, expert-annotated, external Holter ECG recorder. Fifty (50) participants with suspected paroxysmal or persistent atrial fibrillation who had been implanted with a BioMonitor were additionally equipped with an external Holter ECG recorder.

Of these 50 participants, 27 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 131 AF episodes were annotated from 2132.9 hours of Holter ECG data. During the execution of the AF Detection study, only one subject had missing Holter data, and hence was excluded from the analysis. These sensitivity values were used to calculate the 10,000-sample bootstrap (with 71 of 520 replacement) 95% confidence interval for AF detection sensitivity. The 95% confidence limits were 88.5 and 99.1%. The lower 95% confidence interval for AF episode sensitivity of 88.5% clearly exceeds the lower 95% confidence interval for AF episode sensitivity of >60% requested by FDA.

1.3.4 Previous Experience with the BioMonitor 2

A pilot study of the BioMonitor 2-AF device and associated tools/accessories has been completed in Australia. The study followed an open, prospective, single-arm, non-randomized design. The objective of this study was to provide clinical data of the insertion procedure in an electrophysiology or cardiac catheterization laboratory setting, and sensing quality of BIOTRONIK's second generation of ICM, the BioMonitor 2. Data of 30 subjects from 5 Australian clinical sites from December 18, 2014 through July 06, 2015 are included in this summary. There were 22 male and 8 female subjects enrolled with a mean age of 63 years. The most common indications for insertion of the BioMonitor 2 were syncope and symptomatic or asymptomatic atrial fibrillation.

The median time between first skin cut to final successful positioning of BioMonitor 2 was 2.5 minutes. The mean time of the entire implantation procedure was 9.9 minutes. Implanting investigators evaluated the tunneling procedure using the fast insertion tool (FIT) set comprised of FIT 1 (pocket tool) and FIT 2 (lead support tool). The FIT 1 tool was evaluated related to the needed force and grip on the tool, which resulted in a rating of good or acceptable in 83% and 100% of the cases respectively. The FIT 2 tool was evaluated by the implanting investigator for device loading, insertion, removal and overall handling. All assessments were good or acceptable.

The mean R-wave amplitude at the 1-week and 1-month follow-up visit was 0.7 ± 0.4 mV and 0.8 ± 0.4 mV, respectively. The results show significant superiority to the mean R-wave amplitude of the predecessor BioMonitor (0.3 mV). The mean noise burden was 1.3 ± 2.3 % and 2.3 ± 3.1 % at the 1-week and 1-month follow-up, respectively. The results are significantly improved compared to the predecessor device (5.5%). Five subjects reported pain in the pocket during the first week after insertion. Medical treatment was not needed. One subject had a wound infection which was treated with oral antibiotics.

The results demonstrate safety and efficacy of the insertion procedure and the study device. There were no observations of pocket enlargement or device migration during the human clinical evaluation.

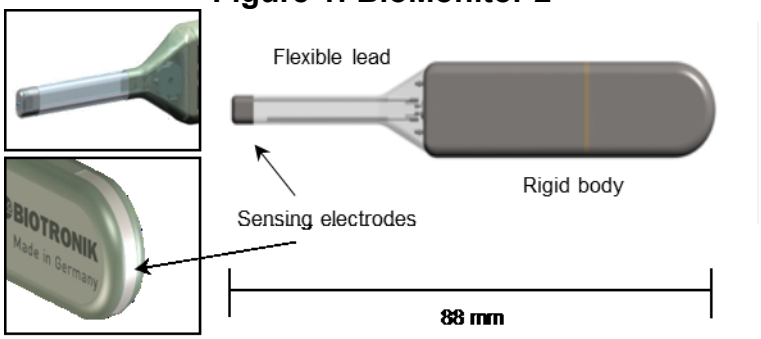
1.4 DEVICE DESCRIPTION

1.4.1 BioMonitor 2 Device Information

BIOTRONIK's second generation ICM, BioMonitor 2, is a programmable, subcutaneous device that monitors multiple parameters used for cardiac arrhythmia identification. In conjunction with BIOTRONIK's Renamic/ICS 3000 Programmer and U.S. market-released CardioMessenger® devices capable of communicating with the BioMonitor 2, the BioMonitor 2 is designed to automatically provide information on the occurrence of arrhythmias in a patient. The BioMonitor 2 is significantly smaller than its predecessor and has a longer vector length, or electrode spacing. Although its pacemaker shaped predecessor achieves good signal quality by intelligent combination of three smaller sensing vectors, the signal amplitudes detected by BioMonitor 2 are generally larger due to the increased vector size.

As seen in Figure 1 below, the BioMonitor 2 is comprised of a flexible lead with an embedded antenna and a rigid body.

Figure 1: BioMonitor 2



The structure and material combination allow for ideal device placement that is adjustable to individual patient anatomy. The rigid portion measures 55 mm and the flexible portion measures 33 mm in length for a full device length of 88 mm. The device is 15 mm wide, 6.2 mm thick, weighs 10.1 g, and is 5 cc in volume. The new shape and

the smaller dimensions of BioMonitor 2 allow for significantly smaller incision length (approx. 15 mm) compared to the predecessor (approx. 40 mm) and parasternal placement, which is located closer to the heart than a typical pacemaker pocket.

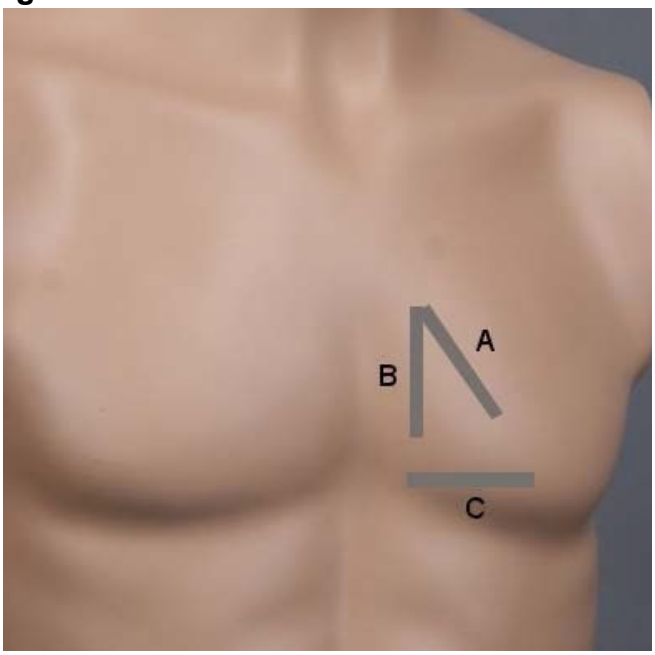
1.4.2 Insertion Procedure

The BioMonitor 2 system is comprised of a specialized FIT set, consisting of the FIT 1 (pocket tool) and FIT 2 (lead support tool), for easy sub-dermal insertion. The insertion tool set (as shown in Figure 2) is designed to create a snug pocket for BioMonitor 2, to have an ergonomic contour for the physician, and to properly support the flexible lead during insertion.

Figure 2: BioMonitor 2 Insertion Tool Set

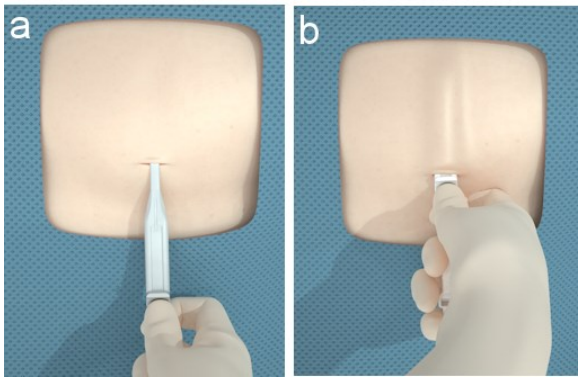
BioMonitor 2 is developed for the insertion into a subcutaneous pocket, in the left side of the chest. The determined positions are based on the patient's anatomy and comfort, as well as cosmetic considerations. Recommended locations are areas where minimal device movement due to positional changes or body and arm movement is expected (Figure 3), e.g. locations between the suprasternal notch and the left nipple, generating an approximately 45° rotation from the midline (position A) or the left parasternal region (position B). Alternatively, a left sub-mammary position can be used (position C).

Figure 3: Possible Positions of BioMonitor 2



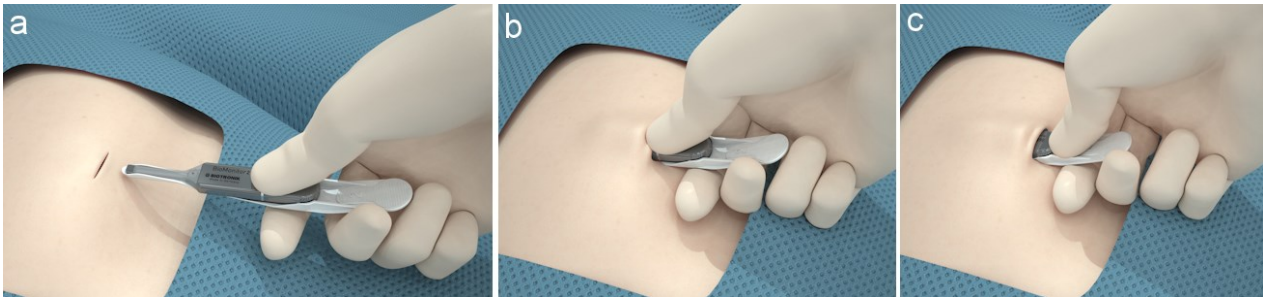
In the selected anatomical position, after application of local anesthetic agent, a small incision through the skin is made, avoiding damage to any underlying musculature. The incision should be approximately 15 mm wide. The pocket tool (FIT 1) is advanced within a sub-dermal plane until the thumb stop approaches the incision, as shown in Figure 4a and 4b. After withdrawing the FIT 1 a suitable pocket for the device is formed.

Figure 4: Insertion of the Pocket Tool FIT 1



The BioMonitor 2 is placed into the support tool, FIT 2, (Figure 5a) and inserted in a two-step approach: First the BioMonitor 2 is gripped with the thumb on top of the device until it is inserted up to the welding line (Figure 5b). In a second step, the device is pushed in with the thumb resting behind the device (Figure 5c). This ensures that both, the FIT 2 with the BioMonitor 2, are inserted together straight into the pre-shaped pocket.

Figure 5: Insertion of the BioMonitor 2 with the Support Tool FIT 2



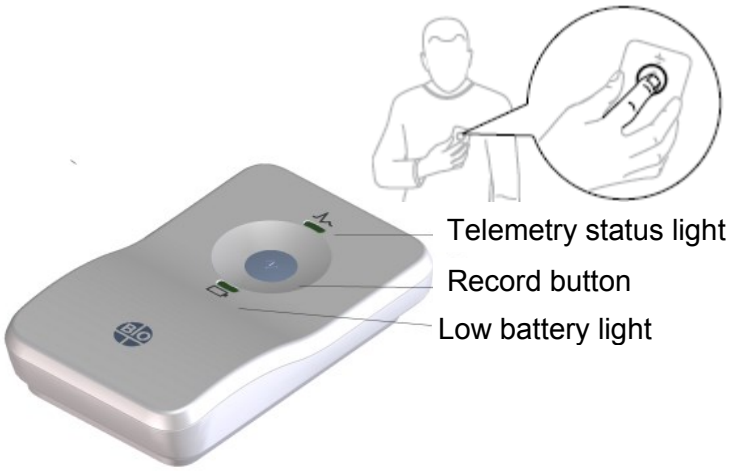
While sliding the support tool FIT 2 out of the pocket, finger pressure is applied to the BioMonitor 2 to keep the device in place. For incision closure standard clinical practice is advised. The protection of the wound from environmental influences according to physician preference finalizes the insertion procedure of BioMonitor 2.

1.4.3 Remote Assistant for Patient Triggering

Many generations of pacemakers as well as the first generation BioMonitor offer the possibility to trigger an IEGM or ECG recording, respectively, if a magnet is applied over the device. The disadvantage of a magnet is its weight and furthermore the patient receives no feedback if the recording was successful or not. Instead, BioMonitor 2 utilizes a small electronic patient device, the Remote Assistant.

The Remote Assistant patient device is a hand-held, battery-operated device which uses radio-frequency and coil telemetry to communicate with the BioMonitor 2. The Remote Assistant is intended for unsupervised patient use away from a hospital or clinic to allow the patient to activate storage of cardiac data when a symptomatic event occurs or has occurred. The Remote Assistant, shown in Figure 6, activates the data management features in the BioMonitor 2 to initiate recording of cardiac event data in the device memory by the single, user-operated button located on the middle area of the Remote Assistant patient device.

Figure 6: Remote Assistant Patient Device

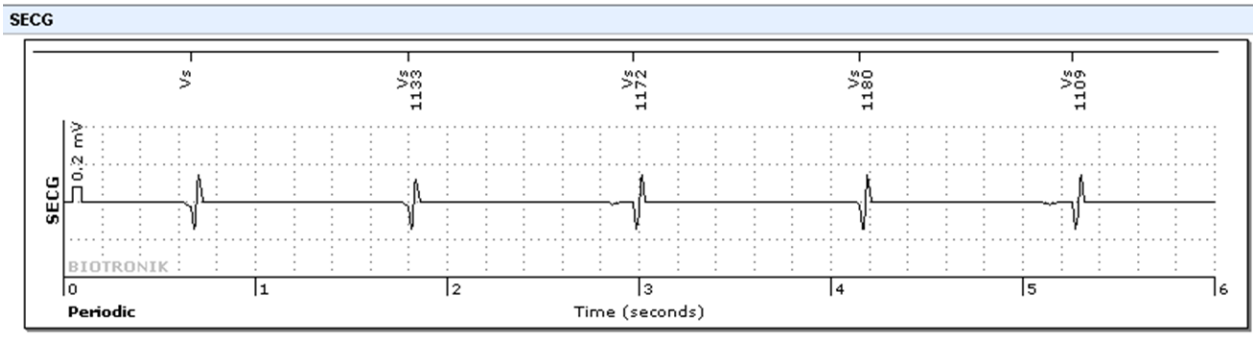


When device is placed over the location of the BioMonitor 2 implant and the record button is pressed, the Remote Assistant indicates if telemetry with the device is successful by briefly displaying a yellow light signal. The patient can then move the Remote Assistant away from their chest and view the green light signal indicating a successful recording.

1.4.4 BIOTRONIK Home Monitoring®

The BIOTRONIK Home Monitoring® system provides early detection of arrhythmic events like high ventricular rates or syncope and of silent, asymptomatic events like atrial fibrillation, through the transmission of periodic (Figure 7) and triggered sECG recordings.

Figure 7: Periodic sECG Transmission Example



The BioMonitor 2 has the capability to transmit messages to the BIOTRONIK Home Monitoring Service Center daily so that the responsible 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 2 and can process them into graphical and tabular format. This information helps the physician optimize the therapy process, as it allows the patient to be scheduled for additional clinical appointments between regular follow-up visits if necessary.

Figure 8: BIOTRONIK Home Monitoring® Transmission Path

BIOTRONIK conducted the TRUST study to evaluate the safety and effectiveness of BIOTRONIK Home Monitoring®. BIOTRONIK received FDA approval (P050023/S020, approved May 12, 2009) of the following labeling claims regarding BIOTRONIK Home Monitoring®:

1. BIOTRONIK Home Monitoring® information may be used as a replacement for device interrogation during in office follow up visits.

2. A strategy of care using BIOTRONIK Home Monitoring® with office visits when needed has been shown to extend the time between routine, scheduled in office follow ups of BIOTRONIK implantable devices in many patients. BIOTRONIK Home Monitoring® data is helpful in determining the need for additional in office follow up.

3. BIOTRONIK Home Monitoring® patients—who are followed remotely with office visits when needed—have been shown to have similar numbers of strokes, invasive procedures and deaths as patients followed with conventional in office follow ups.

4. BIOTRONIK Home Monitoring® provides early detection of arrhythmias.

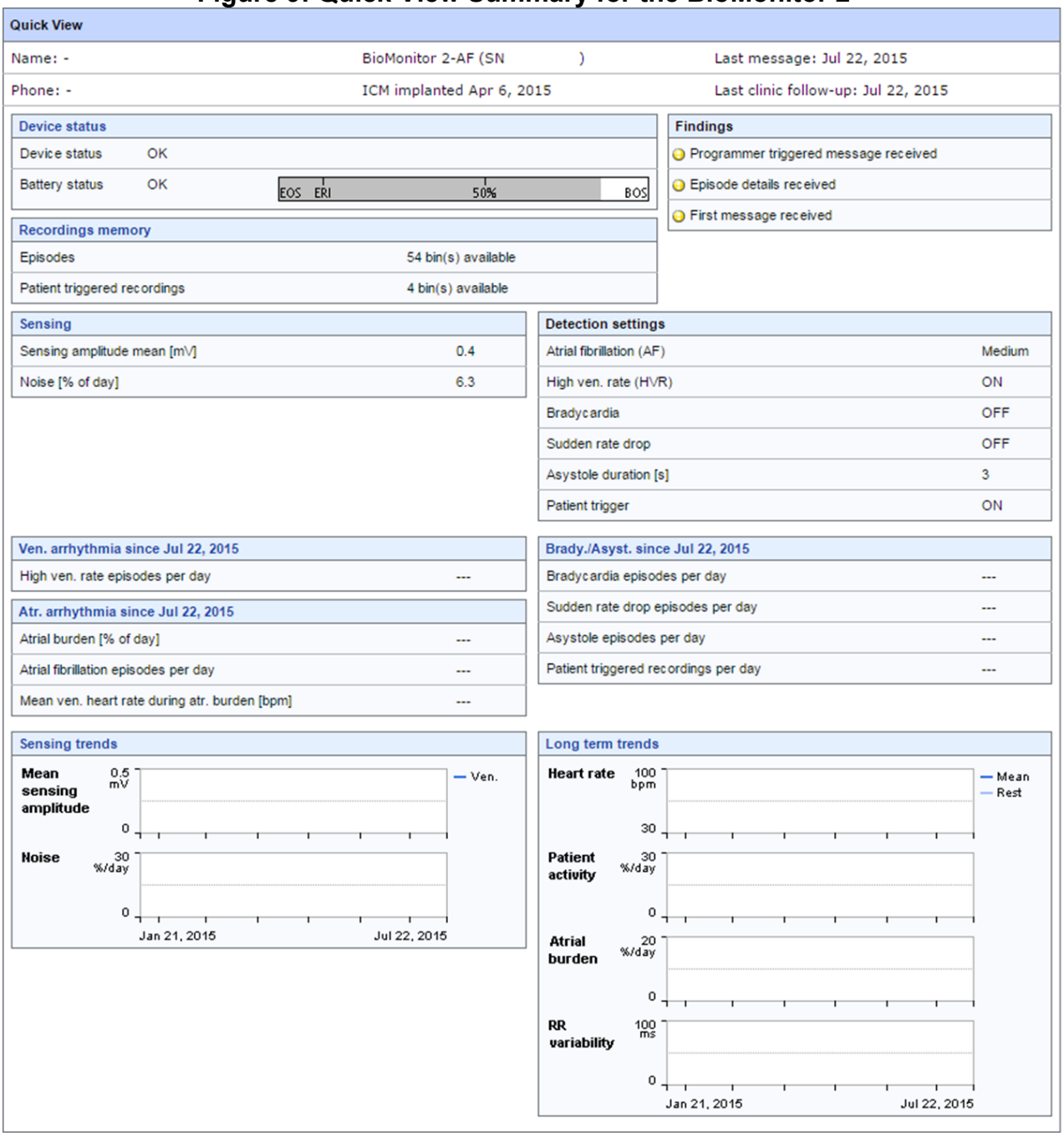
5. BIOTRONIK Home Monitoring® provides early detection of silent, asymptomatic arrhythmias.

6. Automatic early detection of arrhythmias and device system anomalies by BIOTRONIK Home Monitoring® allows for earlier intervention than conventional in office follow ups.

7. BIOTRONIK Home Monitoring® allows for improved access to patient device data compared to conventional in office follow ups since device interrogation is automatically scheduled at regular intervals.

In current US market released BIOTRONIK devices, BIOTRONIK Home Monitoring® provides event and system information similar to what is currently available during office follow-up visits. The BIOTRONIK Home Monitoring® Quick View Summary Report, Figure 9, displays rate trends and episode updates with parameters that are transmitted every 24 hours. These parameters include technical parameters (battery status, sensing amplitudes, and the percentage of noise per day) as well as physiological parameters (heart rate, heart rate variability, patient activity) and arrhythmia parameters (atrial burden, ventricular heart rate during atrial burden, and the number of episodes).

Figure 9: Quick View Summary for the BioMonitor 2



Quick View

Name: -	BioMonitor 2-AF (SN)	Last message: Jul 22, 2015
Phone: -	ICM implanted Apr 6, 2015	Last clinic follow-up: Jul 22, 2015

Device status

Device status	OK
Battery status	OK (EOS ERI 50% BOS)

Findings

- Programmer triggered message received
- Episode details received
- First message received

Recordings memory

Episodes	54 bin(s) available
Patient triggered recordings	4 bin(s) available

Sensing

Sensing amplitude mean [mV]	0.4
Noise [% of day]	6.3

Detection settings

Atrial fibrillation (AF)	Medium
High ven. rate (HVR)	ON
Bradycardia	OFF
Sudden rate drop	OFF
Asystole duration [s]	3
Patient trigger	ON

Ven. arrhythmia since Jul 22, 2015

High ven. rate episodes per day	---

Brady./Asyst. since Jul 22, 2015

Bradycardia episodes per day	---
Sudden rate drop episodes per day	---
Asystole episodes per day	---
Patient triggered recordings per day	---

Atr. arrhythmia since Jul 22, 2015

Atrial burden [% of day]	---
Atrial fibrillation episodes per day	---
Mean ven. heart rate during atr. burden [bpm]	---

Sensing trends

Long term trends

2. STUDY DESIGN

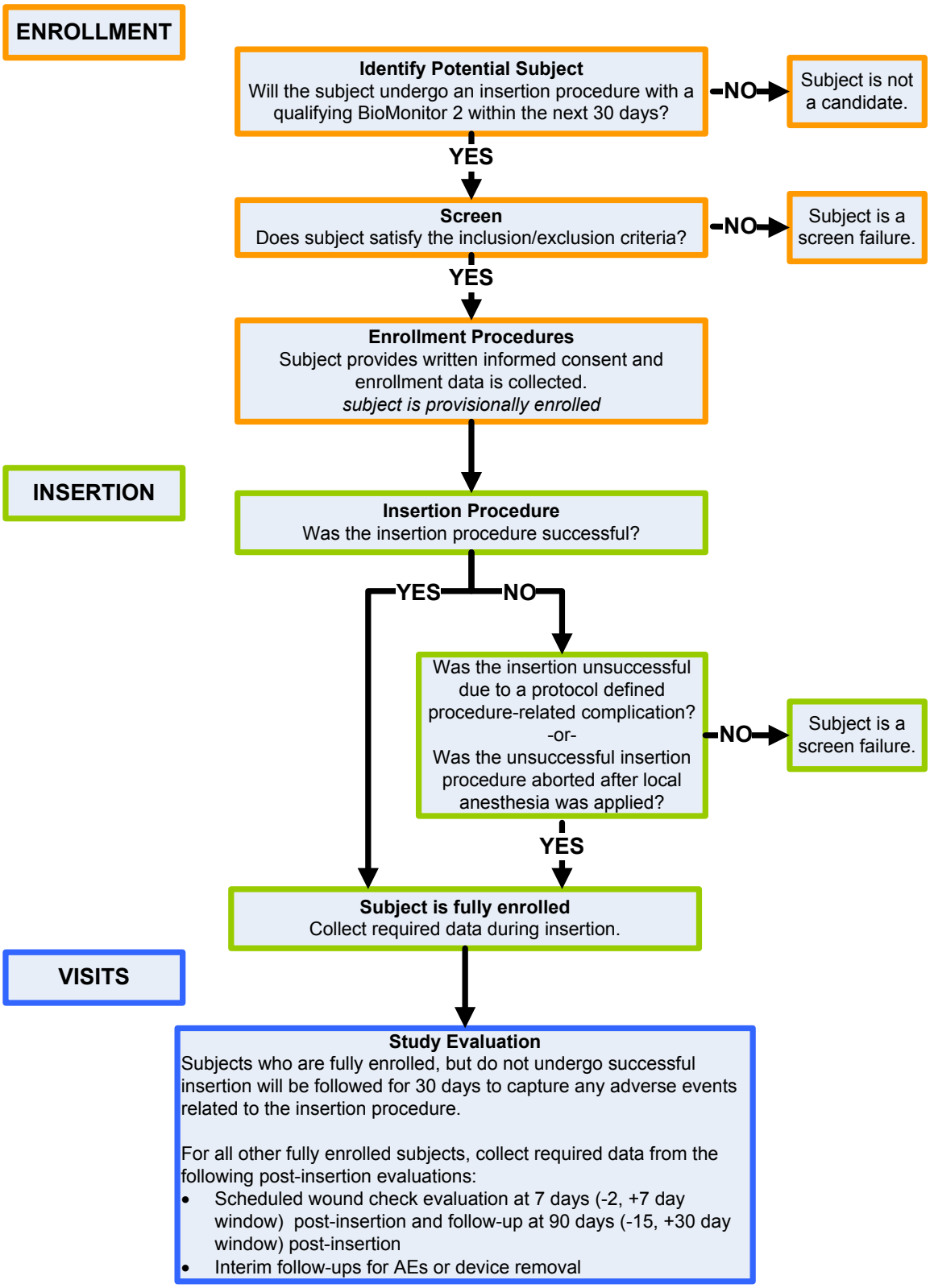
This multi-center, prospective, non-randomized post-market study is designed to evaluate the safety and feasibility of performing the BioMonitor 2 insertion procedure in an office setting. All subjects enrolled in the study will be implanted with a US market released BIOTRONIK BioMonitor 2.

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 ICM. Subjects will be consented within 30 days prior to the insertion procedure and will be screened to ensure they meet all of the inclusion and none of the exclusion criteria as outlined in Sections 3.1.3 and 3.1.4. After eligibility is determined and written informed consent is obtained, subjects will be considered 'provisionally enrolled' until they undergo successful insertion, at which time they are considered fully enrolled. Subjects must undergo insertion within 30 days of provisional enrollment. Subjects who are provisionally enrolled that do not undergo successful insertion within 30 days will be considered screen failures, unless the insertion was unsuccessful due to a protocol defined procedure-related adverse event or the insertion procedure was aborted after local anesthesia was applied. These subjects will be considered fully enrolled and will be followed for 30 days to capture any adverse events related to the insertion procedure. Device data and protocol-defined adverse events will be collected from the date of the first insertion attempt and thereafter through 90 day post-insertion for subjects with successful insertion procedures.

Subjects who undergo successful insertion procedures will be required to complete an initial wound check visit 7 days (window -2, +7 days) after the procedure and a routine follow-up visit at 90 days (window -15, +30 days) post-insertion. Subjects should be seen in-office for all study visits to assess the BioMonitor 2 device and assess for adverse events. For subjects with remote monitoring capabilities, a BIOTRONIK Home Monitoring® report should be used for the device data collected at any study visit; however, the BIOTRONIK Home Monitoring® data must be accompanied with an in-office visit.

Figure 10 provides an overview of the clinical study design. Details of subject eligibility requirements are noted in Section 3.1 and details of other study specific procedures and data collection are noted in Section 3.2 and Section 4.

Figure 10: Study Design Flowchart



2.1 STUDY OBJECTIVES

This study includes the assessment of one primary objective related to the safety of in-office BioMonitor 2 insertions and several secondary objectives related to the associated safety and feasibility. Due to the sample size, there are no pre-specified hypotheses tested in this study.

2.1.1 Primary Objective 1

The purpose of primary objective 1 is to characterize all insertion procedure-related adverse events that require additional invasive intervention to resolve. All adverse events that are considered insertion procedure-related by the investigator will be adjudicated by a Clinical Events Committee (CEC) for classification of the adverse event (as defined in Section 9). The results will be summarized with respect to category and will include event details.

2.1.2 Secondary Objective 1

The purpose of secondary objective 1 is to characterize all insertion procedure-related adverse events that are not included in the primary objective. The results will be summarized with respect to category and will include event details.

2.1.3 Secondary Objective 2

The purpose of secondary objective 2 is to characterize the insertion procedure. This includes the specific device orientation (as defined in Figure 3), final incision size, and total procedure duration. The results will be summarized.

2.1.4 Secondary Objective 3

The purpose of secondary objective 3 is to characterize device functionality post-insertion. This will be achieved by collecting R-wave amplitudes on the day of insertion and at any study visit or through a BIOTRONIK Home Monitoring® report if applicable. Long-term trends available through BIOTRONIK Home Monitoring® will also be used to characterize device functionality through the 90-day study period. The results will be summarized and statistically analyzed, where appropriate.

2.1.5 Additional Data of Interest

Additional information may be collected to characterize the study population, implanted system, insertion procedure, and progress of the study. When available, the collected information may include baseline demographics, medical history, implanted system information, device removals, returned product analysis, and compliance. Specifically, data of interest may include:

- Baseline demographics, including age, gender, weight, height, New York Heart Association (NYHA) class, ejection fraction, and race and ethnicity (optional)
- Medical history, including indication for device

- Implanted device information, including date of insertion and serial numbers for the BioMonitor 2 device and accessories
- Noise burden
- Triggered sECGs
- Investigator assessment of appropriate sECG classification
- Resources used during the insertion procedure
- Overall physician satisfaction and experience with in-office procedures
- All other protocol-defined adverse events excluded from primary objective 1 and secondary objective 1
- Removal experience, if applicable
- Results from returned product analysis
- Compliance to protocol requirements and study visit schedule

When reporting medical history for most recent ejection fraction and the current NYHA class, details regarding the assessments must be obtained within 6 and 3 months prior to enrollment respectively.

2.2 STUDY SIZE AND DURATION

During this study, data will be gathered, analyzed, and reported to evaluate the safety and feasibility of the BioMonitor 2 in-office insertion procedure. It is anticipated that 75 subjects will be implanted and followed through a 90 day post-insertion at up to 7 US sites with up to 20 subjects at each site.

2.3 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 in order to ensure a representative and statistically meaningful sample.

Table 1 demonstrates the precision in estimating the primary objective 1 adverse event rate with the sample size of 75 subjects.

Table 1: Precision in Estimating Adverse Event Rates: Exact 95% Confidence Intervals

Number of Events	Rate	Confidence Intervals (CI)
1	1.3%	(0.0%, 7.2%)
2	2.7%	(0.3%, 9.3%)
3	4.0%	(0.8%, 11.3%)
4	5.3%	(1.5%, 13.1%)
5	6.7%	(2.2%, 14.9%)
6	8.0%	(3.0%, 16.6%)
7	9.3%	(3.8%, 18.3%)
8	10.7%	(4.7%, 20.0%)
9	12.0%	(5.6%, 21.6%)
10	13.3%	(6.6%, 23.2%)
20	26.7%	(17.1%, 38.1%)

The sample size required to assess primary objective 1 is based on an exact, point estimate and one-sided upper 95% confidence interval. The sample size for primary objective 1 was calculated based on the following assumptions:

The standard normal approximation to the 95% confidence interval associated with an estimate of a binomial parameter (p) is given by:

$$95\%\ \text{Confidence Interval:} \quad p \pm 1.96\ [\, p\,(1-p)\,/\,n\,]^{1/2}$$

For example, if there were 4 adverse events out of 75 cases, the observed adverse event rate would be 5.3% and the exact binomial calculation would result in a 95% CI of (1.5%, 13.1%).

2.3.1 Replacement of Subjects

A maximum loss to follow-up of 2% of the total sample size is estimated. The attrition rate encompasses all cases of subject exits prior to study completion, and will include any subject exits. This includes death, device explants, subject directed withdrawals, physician-directed withdrawals, and loss of contact with the subject. Subjects who are provisionally enrolled that do not undergo insertion and are considered screen failures are not included in attrition. In order to ensure a sufficient population size for data analysis, subjects who exit prior to insertion or are determined to be screen failures may be replaced as long as enrollment is ongoing. This includes subjects who were determined to be ineligible for insertion or withdrew from the study prior to the application of local anesthesia during the insertion procedure. These subjects do not count toward the overall planned subject number of 75.

2.4 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.

2.4.1 Objective Analysis

Primary objective 1 will be assessed by performing an exact, point estimate and one-sided upper 95% confidence interval for the rate of insertion procedure-related adverse events requiring invasive intervention within 90 days of insertion. All p-values of 0.05 or lower will be considered evidence of statistical significance.

Secondary objective 1, which includes all other procedure-related AEs that are excluded from primary objective 1, will be summarized with respect to categorized AE rates with their associated, exact, 95% confidence interval.

Other secondary objectives, which include 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. With respect to device functionality, values will also be grouped by visit (enrollment, 90-day follow-up, and interim follow-ups as appropriate).

2.4.2 Trend Analyses

The primary objective is assessed at 90 days post-insertion using a point-estimate and one-sided upper 95% confidence interval. The Kaplan-Meier survival curve method will be used to estimate the adverse event rate at 90 days post-insertion procedure if at least 1 event is observed. Root causes for any failures, regardless of the incidence rates, will be investigated. Long-term device functionality trends may be collected and analyzed from available BIOTRONIK Home Monitoring® reports from insertion through the 90-day follow-up.

2.4.3 Missing Data

All possible steps will be taken to minimize missing data in the study. This includes but is not limited to monitoring of study forms for completeness and supporting efforts to track and maintain contact with study subjects during the follow-up period.

The reasons for any missing data in the study will be documented. In cases of missing device data, BIOTRONIK Home Monitoring® will be used to impute the missing data points. When available, missing data will be imputed with BIOTRONIK Home Monitoring® values obtained from the device on the day of a completed follow-up, target date of a missed follow-up, or the next closest day in the visit window.

With respect to the assessment of the primary objective, only subjects who experience an adverse event associated with the insertion procedure that requires invasive intervention to resolve will be compared to subjects that complete the 90-day follow-up. The secondary objective, which includes other AEs associated with the insertion procedure excluded from the primary analyses, will be assessed in a similar manner. There will be no imputation for these missing adverse event outcomes. Home Monitoring® reports will be accepted for device data to support the secondary objectives in the event that the subject is lost to follow-up.

3. PROTOCOL REQUIREMENTS

3.1 SUBJECT POPULATION

The investigator is responsible for screening all potential subjects and selecting those who are appropriate for study inclusion. Potential subjects will be evaluated against 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 same inclusion and exclusion criteria.

3.1.1 Indications

The BioMonitor 2 is an ICM 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 2. 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 study, the inclusion criteria at the time of subject enrollment include the following requirements:

- Indicated for continuous monitoring with an insertable cardiac monitor
- Willing to be implanted in an office setting with only local anesthetic available
- Able to understand the nature of the study and provide informed consent
- Able and willing to complete all routine follow-up visits at the study site for the expected 90-day follow-up
- Able and willing to use a CardioMessenger® capable of communicating with the BioMonitor 2
- Age greater than or equal to 18 years

At the time of insertion, the following pre-procedure criteria must be met for the subject to undergo insertion:

- Most recent INR value (within 7 days) is less than 3.5 if currently taking warfarin
- Absence of infection with no history of infection within the last 30 days

3.1.4 Exclusion Criteria

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

- Compromised immune system or at high risk of developing an infection
- Abnormal thoracic anatomy or scar tissue at the implant site that may adversely impact the insertion procedure
- Enrolled in any investigational cardiac device trial
- Currently indicated for or implanted with a pacemaker, ICD device, or hemodynamic monitoring system
- Currently implanted with an ICM or ILR
- Life expectancy less than 6 months
- Patients reporting pregnancy at the time of enrollment

3.2 STUDY PROCEDURES

Subjects will be fully enrolled at the time of insertion of a BIOTRONIK BioMonitor 2 ICM. BIOTRONIK Home Monitoring® should be activated in all subjects. All subjects must be seen in-office for all follow-up intervals regardless of remote monitoring activation, but the device data should be provided via BIOTRONIK Home Monitoring®. Device data from BIOTRONIK Home Monitoring® should be chosen from a transmission on or before the date of the in-office visit, no more than seven days prior to the date of visit. Additionally, subjects with unsuccessful insertion procedures as outlined in Section 3.2.3 will be followed for a period of 30 days to capture any adverse events related to the insertion procedure. At the end of the 30-day safety period, a follow-up visit or phone call will be required to assess for adverse events.

Study Procedure Visits:

- Enrollment (subjects are considered provisionally enrolled until undergoing insertion)
- Insertion
- Wound check visit 7 (window -2, +7) days post-insertion
- Routine follow-up evaluations at 90 (window -15, +30) days post-insertion
- Interim evaluations

Table 2 summarizes the visit assessment schedule.

Table 2: Study Visit Assessment Schedule

	Enrollment	Insertion[1]	Wound Check Visit[2]	90-day Follow-up[2]	Interim Evaluation (if applicable)[2,3]
Informed Consent (enrollment)	X				
Demographics and Medical History	X				
Implant Information with Device Evaluation		X[4]			
Device Evaluation			X	X	X
Device Data Read Out				X[5]	
Triggered Events			X	X	X
Adverse Event Assessment		X	X	X	X
Complete eCRF	X	X	X	X	X

[1]Insertion must be completed within 30 days of provisional enrollment/informed consent.

[2]Subjectsusing BIOTRONIK Home Monitoring® should provide device data via BIOTRONIK Home Monitoring® for any study visit, but still must be seen in-office for AE assessment

[3]Interim follow-up information is collected as defined in 3.2.5.

[4]If the insertion procedure is unsuccessful due to a procedure-related adverse event or is aborted after anesthesia is applied, the subject will be followed for a period of 30 days to capture any adverse events related to the insertion procedure.

[5]Detailed instructions provided in Appendix B.

3.2.1 Study Pre-screening

Prior to enrollment, the patient's medical history must be reviewed in order to ensure they are an appropriate candidate for the study. Subjects taking any oral anticoagulant (OAC) may be asked to hold their medication prior to the insertion procedure at the discretion of the implanting physician. In addition, all patients must satisfy the study inclusion and exclusion criteria prior to enrollment, including being a candidate for a BIOTRONIK BioMonitor 2 ICM.

3.2.2 Enrollment Visit

If the patient has been determined to be eligible for the study, informed consent must be obtained from the patient prior to initiating any study related procedures. The consent process, including discussion of the study, should be documented in the patient's medical or study records.

The following data collection and reporting procedures are performed at enrollment:

- Obtain Informed Consent
- Collect subject demographics (gender, height, weight, etc.)
- Medical history of subject, including device implant indications
- Complete all required eCRFs

3.2.3 Insertion

Insertion will take place in an office setting. The insertion may be completed on the same day as informed consent or within 30 days after. If the subject is taking OACs at the time of enrollment, the implanting physician will decide how long they may need to hold their medication and the subject may not be able to undergo the BioMonitor 2 insertion on the same day. BioMonitor 2 will be inserted on the left chest side as described in Section 1.4.2. The physician performing the insertion will also determine the optimal device position for each subject, as described in Figure 3.

Subjects are considered provisionally enrolled until they are successfully implanted with the BioMonitor 2, at which time they are considered fully enrolled. Subjects who are provisionally enrolled that do not undergo successful insertion procedures within 30 days will be considered screen failures, unless the insertion was unsuccessful due to a protocol defined procedure-related adverse event or the insertion procedure was aborted after local anesthesia was applied. These subjects will be considered fully enrolled, included in the intention-to-treat (ITT) population, and followed for 30 days post-insertion to capture any adverse events related to the insertion procedure. At the end of the 30-day safety period, a follow-up visit or phone call will be required to assess for adverse events.

The following data collection and reporting procedures are performed at insertion:

1. Confirm the subject meets the pre-procedure inclusion criteria:
    - Most recent INR value (within 7 days) is less than 3.5 if currently taking warfarin
    - Absence of infection with no history of infection within the last 30 days
2. Collect insertion information.
    - Date of procedure
    - Method and approach including:
        - Device orientation (as described in Figure 3)
        - Final incision size (measured with a suitable tool)
        - Insertion procedure time (measured from incision to last suture)
    - Procedure success
3. Collect device serial numbers for the BioMonitor 2, CardioMessenger®, and Remote Assistant.

4. Record initial R-wave amplitudes as outlined in Appendix B.
5. Record any insertion procedure-related and device-related adverse events during insertion and complete an Adverse Event eCRF. Insertion procedure-related adverse events should be reported even if the insertion attempt is unsuccessful.
6. Program BioMonitor 2 parameters to best suit the needs of the subject.
7. Interrogate and print the final programmed parameters.
8. Complete all required eCRFs.

3.2.4 Wound Check Visit and 90-day Follow-up

Subjects will undergo an assessment of their device at a wound check visit 7 days post-insertion (window -2, +7 days) and a 90-day follow-up after insertion (window -15, +30 days). BIOTRONIK Home Monitoring® transmissions should be used for the device data at any follow-up, including the wound check and 90-day visit; however, an in-office visit to support an AE assessment and other protocol requirements will still be required. Device data from BIOTRONIK Home Monitoring® should be chosen from a transmission on or before the date of the in-office visit, no more than seven days prior to the date of visit.

Each site Principal Investigator (PI) will be trained to identify and schedule follow-ups to meet the required expectation. Additionally, the Electronic Data Capture (EDC) system will provide assistance in identifying properly scheduled follow-up visits according to this protocol.

The following study procedures are performed at the wound check visit and 90-day in-office follow-up:

1. Obtain BIOTRONIK Home Monitoring® Cardio Report from a transmission on or before the date of the in-office visit, and within seven days prior to the date of visit if available.
2. Activate the Remote Assistant and wait approximately 2 minutes.
3. Interrogate the BioMonitor 2 and print initial programmed parameters and view stored diagnostic data.
4. Record the daily average R-wave amplitudes and corresponding date through BIOTRONIK Home Monitoring®. If BIOTRONIK Home Monitoring® is not available, record the R-wave amplitudes as described in Appendix B.
5. Record the daily average noise percentage through BIOTRONIK Home Monitoring®. If BIOTRONIK Home Monitoring® is not available, record the noise percentage as described in Appendix B.
6. If there have been any triggered events or alerts since the subject was last seen, not including the recording triggered at the visit:
   - Evaluate cause of patient triggers.

- For non-patient triggers, determine if the rhythm associated with the trigger classification is able to be confirmed, when possible, using methods such as surface ECG verification, symptoms indicative of rhythm, etc. If any triggers were suspected to be inappropriate, document the suspected reason(s).

7. Determine if there have been any adverse events (as defined in Section 9). If any are recorded, complete an Adverse Event eCRF.
8. Program other parameters to best suit the needs of the subject.
9. At the 90-day follow-up visit perform a device data “Read out” to print and store the BioMonitor 2 data as described in Appendix B.
10. Interrogate and print the final programmed parameters.
11. Review and complete the appropriate eCRFs.

3.2.5 Interim Follow-ups and System Revisions

Interim follow-ups may occur anytime during the study, at the request of the investigator or subject, as a result of a triggered sECG or BIOTRONIK Home Monitoring® alert, etc. Anytime a subject’s device is interrogated for any reason during the 90-day study period, data should be collected (as outlined in Section 3.2.4) and an interim Follow-up eCRF completed. In the event of a subject evaluation to assess for a protocol-defined adverse event, in which a device interrogation does not occur, an interim Follow-up eCRF does not need to be completed, but adverse event data should be captured on the Adverse Event eCRF. Other hospital or clinic visits that are unrelated to the device or insertion procedure are not required to be collected.

Any system revision that is performed after successful insertion of the device but prior to the 90-day follow-up has to be documented in the study. A system revision is defined as any reposition or removal of the original inserted BioMonitor 2. In the event of a system revision, a System Revision eCRF is required as well as the following data:

- Reason for reposition or removal
- Date of reposition or removal
- Type of revision
- Location of revision (clinic, hospital, office, etc.)
- Outcome of revision (including type of replacement and device manufacturer, if applicable)

In the event of a reposition, the new device orientation will also be collected.

4. DATA COLLECTION

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 access to reports for BIOTRONIK, specified study sites, and any other parties authorized by BIOTRONIK.

4.2 ELECTRONIC CASE REPORT FORMS (ECRFS)

Original data will be collected at each study site and recorded into the EDC system. BIOTRONIK will audit source data and monitor completed investigator locked eCRFs. The investigator will be required to use an electronic signature to approve the content of the data reported in the eCRFs.

Information from electronically delivered source data (e.g. programmers) will be captured and stored in a validated environment.

Subject follow-up is required for all subjects fully enrolled in this clinical study. The required follow-up visit dates are based on BioMonitor 2 insertion date, and are to be used for the calculation of the dates of the routine follow-up schedule. The following eCRFs will be available in the EDC system:

- Informed Consent
- Informed Consent Update
- Enrollment
- Insertion
- Wound Check Visit (-2, +7 day window)
- 90-day Follow-up (-15 , +30 day window)
- Interim Follow-up
- Adverse Event
- System Revision
- Study Exit
- Protocol Noncompliance
- Data Clarification

4.3 DATA CLARIFICATION/DATA QUALITY CONTROL

BIOTRONIK will review study data. At any time, reports can be generated on data completion and missing data for each study site. An 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 as well as to identify data completed, due, overdue, and backlogged. In addition, all study data will undergo automatic edit and plausibility checks, which provide 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 study sites, BIOTRONIK monitors will conduct monitoring visits (see Section 7).

To ensure compliance with federal regulations, internal policies and procedures, and the study protocol, the EDC vendor will routinely be monitored and/or audited by BIOTRONIK or a BIOTRONIK representative as required by BIOTRONIK standard operating procedures (SOPs).

4.4 SUBJECT RETENTION

Due to the relatively small population size, subject attrition is not considered to be a challenge. A maximum loss to follow-up of 2% of the total sample size is estimated. BIOTRONIK will provide additional tools to the sites in an effort to minimize the number of subjects that are lost to follow-up. The EDC system includes an overview of each subject's follow-up schedule, including the windows for each follow-up. The EDC system also provides a subject follow-up tool in the form of a Follow-up Compliance Detail Report. This report allows research personnel to become alerted to and track all study subjects that should be scheduled for upcoming follow-ups.

4.5 SUBJECT DATA CONFIDENTIALITY

All information sent to BIOTRONIK pertaining to each subject will be kept confidential at BIOTRONIK and is subject to FDA audit. Source documents used to support study objectives adjudication by the CEC will have all confidential subject identifiers redacted prior to being provided to the CEC. Reports submitted to the physician and publications of study results will not make any reference to subject names.

In order to verify the study data and ensure study integrity, monitors from BIOTRONIK, the FDA, and the reviewing Institutional Review Board (IRB) may review and/or copy the study records.

5. RISKS AND RISK MINIMALIZATION

All devices included in this study are legally marketed and being prescribed by physicians according to FDA approved indications for use.

As with any implantable device, there are always potential risks that accompany the device. The following list provides the potential risks that may occur with the use or insertion of the BioMonitor 2:

- Device failure
- Device migration
- Device rejection phenomena (including local tissue reaction)
- Excessive bleeding
- Fluid accumulation within the device pocket
- Hematoma
- Infection
- Pocket pain
- Skin erosion

These risks can be minimized through use of strict aseptic technique, compliance with the study protocol and technical insertion procedures, adherence to the guidelines for selection of subjects, close monitoring of the subject's physiologic status during insertion and follow-up procedures, and by promptly supplying BIOTRONIK with all pertinent information required by this protocol.

As excessive bleeding is of particular concern with in-office procedures, subjects taking warfarin or any other OAC may be asked to hold their medication prior to the insertion procedure at the discretion of the implanting physician.

BIOTRONIK foresees no additional risks associated with this study beyond those stated in the labeling for device.

6. STUDY ORGANIZATION

6.6 SPONSOR

BIOTRONIK is the "sponsor" of the BioInsight Study. A "sponsor" is defined as an entity that initiates but does not conduct a study. BIOTRONIK's responsibility as the clinical study sponsor is to ensure protocol and regulatory compliance through proper monitoring of the study. BIOTRONIK is required to ensure that the device is used under the immediate direction of an investigator. As the investigator, the physician is responsible for conducting the study in accordance with the signed agreement, the study protocol, applicable laws, FDA regulations, and any conditions of approval imposed by the reviewing IRB. The primary investigator must also accept responsibility for all aspects of the study including the actions of any co-investigators participating in the study at the study site.

6.7 CLINICAL EVENTS COMMITTEE

A Clinical Events Committee (CEC) consisting of at least 3 independent electrophysiologists will be established to review and adjudicate adverse events that occur during the study. The CEC will be blinded to the clinical study site and subject identity, and to minimize bias, members will not participate as investigators. The CEC will create a study specific charter defining the adverse event adjudication process, specifically detailing review guidelines along with appropriate response timelines.

All protocol defined adverse events (see Section 9.1) will be adjudicated by the CEC. The CEC will classify the adverse event and indicate whether the adverse event is related, possibly related, not related, or has an unknown relation to the BioMonitor 2 insertion procedure. The CEC will also have the responsibility to adjudicate the type of adverse event (insertion procedure-related, device-related, and non-procedure non-system related) and specific category (Section 9.1).

7. STUDY MONITORING

7.1 SUMMARY

BIOTRONIK's responsibility as the clinical study sponsor is to ensure protocol and regulatory compliance through proper monitoring of the study. BIOTRONIK requires IRB review and a subject Informed Consent Form for all after-market research. Monitoring may be conducted on-site at the study site or remotely by BIOTRONIK monitors.

Through on-site or centralized monitoring, BIOTRONIK will assess the site's performance in the following areas:

- Verification that informed consent was obtained
- Adherence to protocol eligibility criteria and requirements
- Documentation of performed procedures and assessments related to:
  - Study objectives
  - Protocol required safety assessments
  - Evaluating, documenting, and reporting subject deaths and withdrawals, especially when a withdrawal may be related to an adverse event.
- Investigator oversight and delegation of authority to study personnel
- Verification of study-specific required documentation
- Conduct and documentation of procedures essential to trial integrity
- Adherence to the applicable FDA regulations regarding the obligations of the investigator and maintenance of records.

As the investigator, the physician is responsible for conducting the study in accordance with the signed agreement, the study protocol, applicable laws, FDA regulations, and any conditions of approval imposed by the reviewing IRB. The principal investigator must also accept responsibility for all aspects of the study including the actions of any sub-investigators participating in the study at the study site.

7.2 STUDY MONITORS

Study monitors are trained, qualified, and designated by BIOTRONIK management to oversee the progress of a study at the study site. Additional monitors may be appointed as necessary.

The address to submit study information to BIOTRONIK is:

BIOTRONIK, Inc.
Attn: BioInsight Study
Clinical Studies Department
6024 Jean Road
Lake Oswego, Oregon 97035

Study information may also be submitted by fax to: (800) 723-9220

For study assistance, call: (800) 547-0394

For technical assistance 24 hours a day, call: (800) 547-0394

7.3 MONITORING VISITS

A monitor will conduct monitoring visits at study sites in accordance with the Monitoring Plan. Sites are required to support these visits and the study monitoring effort. On-site monitoring visits will also provide an assessment of the continued acceptability of the facilities to continue participation in the study.

7.4 CENTRALIZED MONITORING

Centralized monitoring will be conducted throughout the course of the study in accordance with the Monitoring Plan. Some examples of data that may be monitored remotely include: informed consent forms, insertion and device data, and adverse events reported in the EDC system. Sites are required to support centralized monitoring by providing source documents to BIOTRONIK in order to source data verify data reported in the EDC system and resolving queries in a timely manner.

8. STUDY COMPLETION

BIOTRONIK will notify the study site upon completion or termination of the study or investigator's participation in the clinical study. At BIOTRONIK's request, an investigator will return any devices, equipment and pertinent information in their possession. BIOTRONIK will provide a final report to each study site. The investigator must retain records related to the study for a period of 2 years after the study is completed.

9. ADVERSE EVENTS

The rate of insertion procedure-related adverse events (AEs) within 90 days post-insertion that require additional invasive intervention to resolve will be assessed. Additional data will be collected on the safety and feasibility of in-office insertion procedures.

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, or non-procedure non-system related. Only adverse events occurring in fully enrolled subjects on or after the date of insertion through the duration of the study will be collected. If the insertion procedure is unsuccessful due to a procedure-related adverse event or is aborted after anesthesia is applied, the subject will be followed for a period of 30 days to capture any additional adverse events related to the insertion procedure.

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 and non-procedure non-system 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. Detailed information for specific categories is located in Appendix A. Final categories will be determined by the CEC. The CEC charter may include alternate classifications for some adverse events.

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 create pocket
- 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 occur:

- 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

9.2 ANALYSIS OF THE OBJECTIVES

All protocol defined AEs included in the primary and secondary objective analysis will be adjudicated by the Clinical Events Committee (CEC) (see Section 2.1). For each AE, the CEC will classify the relatedness to the insertion procedure as not related, related, possibly related, or unknown. The CEC will also have the responsibility to adjudicate the type (insertion procedure-related, device-related, or non-procedure non-system related) as well as the specific category of each reported AE (see Section 9.1).

In assessment of the primary objective, the estimate of AE rates will be based on the number of subjects with at least one AE adjudicated as related to the insertion procedure as a proportion of total subjects. Events with a final AE adjudication of possibly related, not related or unknown relatedness classification will not contribute to or be included in the assessment of the primary objective. AEs related to the insertion procedure that require additional invasive intervention to resolve are included in primary objective 1. The same rules will be used for purposes of Kaplan-Meier survival analyses, described in Section 2.4.2.

Secondary objective 1, which includes AEs that were excluded from primary objective 1 through 90 days post-insertion, will also be summarized as AE rates along with their associated, exact 95% confidence intervals.

9.3 Adverse Events for the Analysis of the Primary and Secondary Objectives

9.3.1 Adverse Events for the Analysis of Primary Objective 1

If any of the following invasive actions occur in order to resolve an above listed insertion procedure AE, the AE will be included in the primary objective analysis:

- Device removed
- Device replaced
- Device surgically repositioned
- Other surgery performed related to the device or primary insertion procedure

Subject deaths as a result of a BioMonitor 2 insertion procedure-related AE will be included in the primary objective analysis. Additionally, an AE that requires a transfer to a hospital facility during the initial in-office insertion procedure to resolve the AE will be included in the primary objective analysis.

Primary objective 1 will exclude adverse events that do not meet these criteria.

9.3.2 Adverse Events for the Analysis of Secondary Objective 1

All insertion procedure-related AEs excluded from primary objective 1 are included in secondary objective 1 analysis.

9.4 Adverse Event Reporting

The AEs that an IRB considers reportable are dependent on the particular IRB. To avoid underreporting, BIOTRONIK recommends that, at a minimum, the investigator reports insertion procedure-related and device-related AEs, as well as protocol-defined non-procedure non-system related AEs, that occur during the BioInsight Study to BIOTRONIK and the IRB.

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. OTHER GENERAL INFORMATION

10.1 PROTOCOL COMPLIANCE

The investigator is responsible for conducting the study in accordance with the signed agreement, the study protocol, applicable laws, and any conditions of approval imposed by the reviewing IRB. The investigator shall notify BIOTRONIK and the reviewing IRB in writing no later than 5 working days after any significant deviation from the study plan 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 study plan.

BIOTRONIK categorizes protocol noncompliance instances as either violations or deviations. Both protocol violations and deviations will be reported during interim reports.

10.1.1 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
- Subject inclusion/exclusion violations and protocol requirement violations that affect the primary objectives of the study design

These violations will be reported in accordance with applicable regulatory timelines and the site must notify the reviewing IRB per the IRB's reporting requirements. The site should provide a copy of the IRB protocol noncompliance notification (as applicable) to BIOTRONIK. Protocol violations must also be reported to BIOTRONIK via Protocol Noncompliance eCRFs.

10.1.2 Protocol Deviations

Protocol deviations are deviations from the requirements of the protocol in such a manner whereby data is unusable or not available. Protocol deviations are less serious in nature. The site should report protocol deviations of required per the IRB of record. Protocol deviations include, but are not limited to:

- Procedure not performed within the allowed follow-up window
- Required data not obtained

The site must report protocol deviations to BIOTRONIK via Protocol Noncompliance eCRFs. Both protocol deviations and violations will be reported in interim reports.

10.2 STUDY EXITS

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.

10.2.1 Screen Failures

Screen failures, as defined in Section 3.2.3, will be exited in the EDC system. The reason and date of withdrawal will be obtained and a Study Exit eCRF will be completed.

10.2.2 Unsuccessful Insertion Procedures

Subjects with unsuccessful insertion procedures, as defined in Section 3.2.3, will be followed for 30 days post-insertion to capture any complications related to the insertion procedure and then will be exited. The reason and date of withdrawal will be obtained and a Study Exit eCRF will be completed.

10.2.3 Withdrawal of Consent

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

10.2.4 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 reported for any subject death:

- Subject records such as a death certificate, death report signed by the investigator, or other relevant medical records that include the following details:
  - Date of death
  - Place death occurred
  - Immediate cause of death
- Statement whether death was device or insertion procedure-related

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

10.2.5 BioMonitor 2 Removal

Any subject who has the BioMonitor 2 ICM removed during the follow-up will be withdrawn from the study. If the BioMonitor 2 is replaced with another BioMonitor 2, the subject will not continue participation in the study. A Study Exit and System Revision eCRF should only be completed after documentation of the device removal or replacement procedure is available (see Section 3.2.5).

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

10.2.6 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® reports will be accepted for device data to support the secondary objectives in the event that the subject is lost to follow-up.

10.2.7 Study Participation Complete

All subjects who undergo successful insertion procedures are expected to be followed for 90 days post-insertion (window -15, +30 days). After a subject completes their final routine visit in this time interval, their study participation is complete and the subject should be exited from the study by completing a Study Exit eCRF.

10.3 INFORMED CONSENT

Prior to the subject's participation in the study, informed consent is required from all subjects. Informed consent should be obtained in accordance with the FDA regulations (21CFR, Part 50). The investigator is required to inform BIOTRONIK and the reviewing IRB within 5 days if any subject was not appropriately consented to participate in the study. In order to assist with the consent process, BIOTRONIK will provide a template subject consent form to study sites participating in the study.

10.4 IRB APPROVAL

IRB approval is required from each institution prior to participation in this post-market study. Subject enrollment may not begin until 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.

10.5 Other Institutions and Physicians

This post-market study is not transferable to other institutions attended by the investigator unless prior approval is obtained from both BIOTRONIK and the appropriate IRB. Additional study sites may be included in this study but may not exceed the limits set by the protocol. Only approved investigators are authorized to participate in the study. However, there are certain situations where an investigator might not be immediately available to provide the necessary medical care for a subject enrolled in this study (e.g. when a subject goes to the emergency room for medical treatment). In these instances a protocol deviation 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 subject's medical care and rights as a research subject.

11. RECORDS AND REPORTS

11.1 INVESTIGATOR RECORDS

Investigators are required to maintain on file the following accurate, complete and current records relating to this study:

- All correspondence relating to the study with another investigator, an IRB, BIOTRONIK, a monitor, or the FDA, or any other regulatory authority. (e.g., a letter sent from the investigator to the IRB).
- A copy of the study protocol
- Signed investigator or research agreement
- Signed Financial Disclosure Form
- A copy of the IRB letter approving the research study
- A copy of the IRB approved subject Informed Consent Form
- All documentation, including:
  - a copy of the signed subject consent form
  - all supporting documentation for data entered into the EDC system
  - records of any adverse device effect, including supporting documentation
  - records pertaining to subject deaths during the study
  - documentation and rationale for any deviations from the clinical protocol
  - any other records required by BIOTRONIK
  - records of device disposition

11.2 INVESTIGATOR REPORTS

Investigators are required to prepare and submit to BIOTRONIK the following complete, accurate, and timely reports on this study when necessary:

- Notification of a subject death during the study
- Notification of the withdrawal of IRB approval
- Annual progress reports prepared for the IRB
- Notification of any deviations from the study plan
- Notification that an informed consent was not obtained from the subject
- Final summary report prepared for the IRB
- Any other information upon the request of an IRB, FDA, or BIOTRONIK

Table 3 outlines the responsibilities, including time constraints, for submitting the above reports.

Table 3: Investigator Reporting Responsibilities

Type of Report	Report to BIOTRONIK	Report to IRB	Time Constraints of Notification
Subject Death During Study	Required	Required	BIOTRONIK as soon as possible and as required by reviewing IRB
Subject Withdrawal	Required	IRB Dependent	Within 5 working days
Withdrawal of IRB Approval	Required	Required	Within 5 working days
Progress Report	Required	Required	Submitted not less often than yearly
Significant Deviations from Protocol	Required	Required	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	Required	Required	As soon as possible after discovery and no more than 5 working days

11.3 SPONSOR RECORDS

BIOTRONIK will maintain the following records:

- All correspondence that pertains to the study with the investigator(s), IRB, and FDA
- Investigator agreements, financial disclosures, and current curriculum vitae
- Name and address of each investigator and each IRB that is involved with the study
- Adverse events and complaints
- Adverse device effects
- Electronic Case Report Form data
- Clinical study plan and report of prior investigations
- Monitoring reports
- Clinical progress reports

Table 4 outlines the responsibilities, including time constraints, for sponsor reports.

Table 4: Sponsor Reporting Responsibilities

Type of Report	Prepared by BIOTRONIK for	Time Constraints of Notification
Withdrawal of IRB Approval	All reviewing IRBs and participating investigators	Notification within 5 working days of receipt of notice of withdrawal of approval
Progress Report	All reviewing IRBs	A progress report will be submitted at least annually
Recall and Disposition	FDA, all reviewing IRBs	Notification within 30 working days and will include the reasons for any request that an investigator return, repair or otherwise dispose of any devices.
Final Report	All reviewing IRBs and participating investigators	Notification within 30 working days of the completion or termination of the study. A final report will be submitted within 6 months after completion or termination of the study.

12. REFERENCES

[1] Pürerfellner H, et al. Miniaturized Reveal LINQ insertable cardiac monitoring system: First-in-human experience. *Heart Rhythm* 2015;12(6):1113-9.

[2] Mittal S, et al. Safety Profile of a Miniaturized Insertable Cardiac Monitor: Results from Two Prospective Trials. *Pacing and Clinical Electrophysiology* 2015;38(12):1464-9.

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[4] Pakarien S, et al. Short-term implantation-related complications of cardiac rhythm management device therapy: a retrospective single-centre 1-year survey. *Europace* 2010;5:907-25.

[5] Poole JE, et al. Complication rates associated with pacemaker or implantable cardioverter-defibrillator generator replacements and upgrade procedures: results from the REPLACE registry. *Circulation* 2010; 122(16):1553-61.

[6] Hancox JG, et al. The Safety of Office-Based Surgery:
Review of Recent Literature From Several Disciplines. *Arch Dermatology* 2004; 140(11):1379-82.

APPENDIX A: DEFINITION OF TERMS

AE – Adverse Event

AF – Atrial Fibrillation

CEC – Clinical Events Committee

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.

eCRF – Electronic Case Report Form

EDC – Electronic Data Capture system

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

FIT – Fast Insertion Tool

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.

ICD – Implantable Cardioverter Defibrillator

ICM – Insertable Cardiac Monitor

IRB – Institutional Review Board

IRL – Implantable Loop Recorders

ITT – Intention-to-treat

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.

NYHA – New York Heart Association

OAC – Oral Anticoagulant

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.

sECG – Subcutaneous Electrocardiogram

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

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.

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.

Suspected Device Failure – Device issue that is believed to be an electrical malfunction.

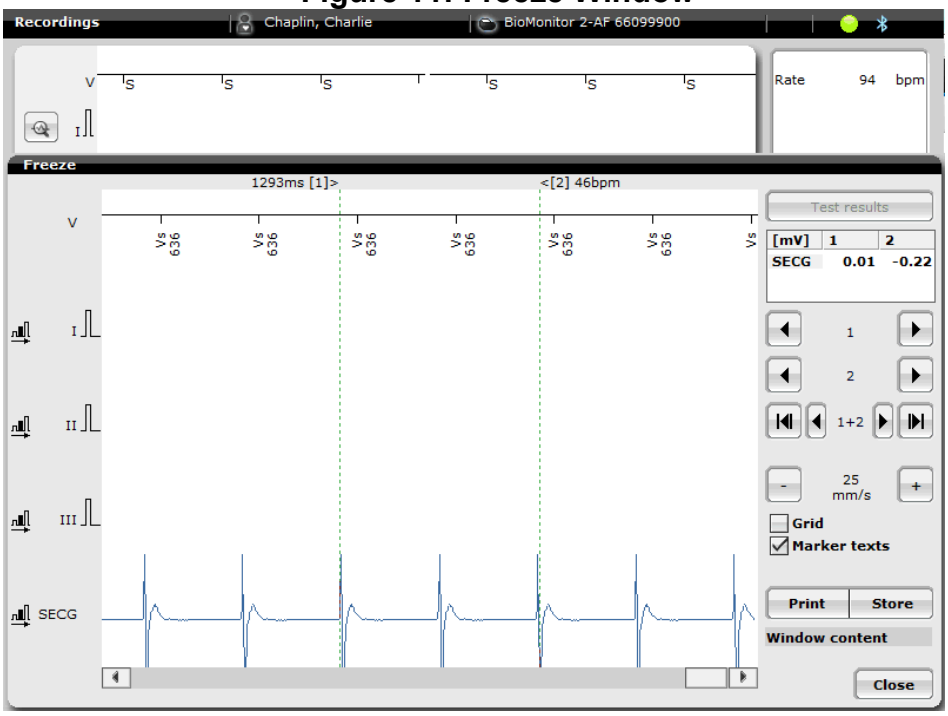
APPENDIX B: DETAILED PROCEDURES

I. Insertion Visit Device Data

R-Wave Amplitudes

- Interrogate the BioMonitor 2
- Freeze window to capture the R-waves as shown in Figure 11 using the "" icon.

Figure 11: Freeze Window



- Provide the peak amplitudes of two R-waves using the calipers. Document the two R-wave amplitudes on a study worksheet or medical record. "Print" and "Store" this Freeze window (at least 25 mm/s).
- While in the Freeze window with the R-waves selected, print a screenshot by following Figure 12. To do this, connect the USB flash drive (orange arrow) to the Programmer USB port. Open left paper tray (green arrow). Press the Stop and the 10 button (blue arrow).

Figure 12: Print Screen Instructions

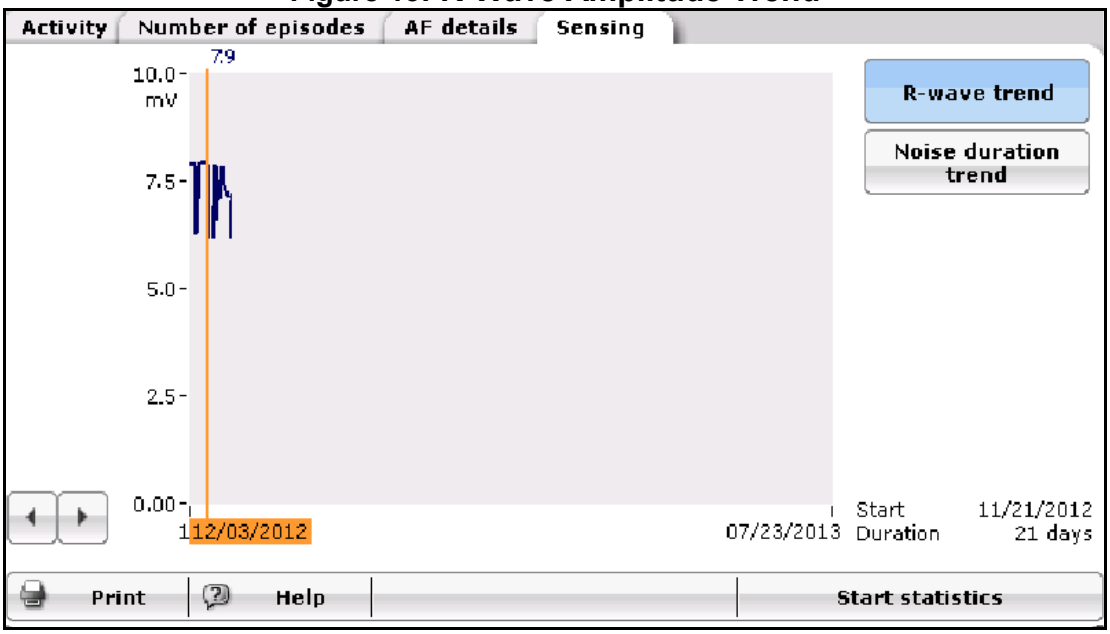
II. Wound Check Visit and 90-day Follow-up visit Device Data

Please follow these steps when BIOTRONIK Home Monitoring® is not available.

Average R-Wave Amplitude

- Under "Diagnostics" → "Sensing" → "R-wave trend," put the caliper on the date of visit, and record the value displayed above the graph with the date of visit selected.

Figure 13: R-Wave Amplitude Trend

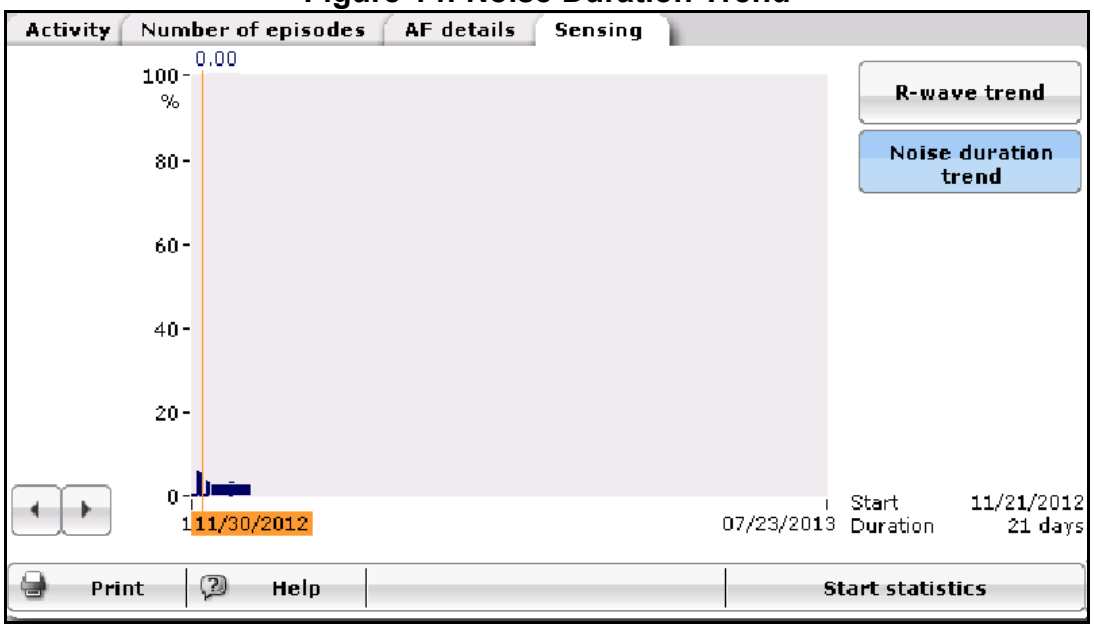


- While in the R-Wave trend window with the date of visit selected, print a screenshot by following Figure 12. To do this, connect the USB flash drive (orange arrow) to the Programmer USB port. Open left paper tray (green arrow). Press the Stop and the 10 button (blue arrow).

Average Noise Burden

- Under "Diagnostics" → "Sensing" → "Noise duration trend," put the caliper on the date of visit, and record the value displayed above the graph with the date of visit selected.

Figure 14: Noise Duration Trend



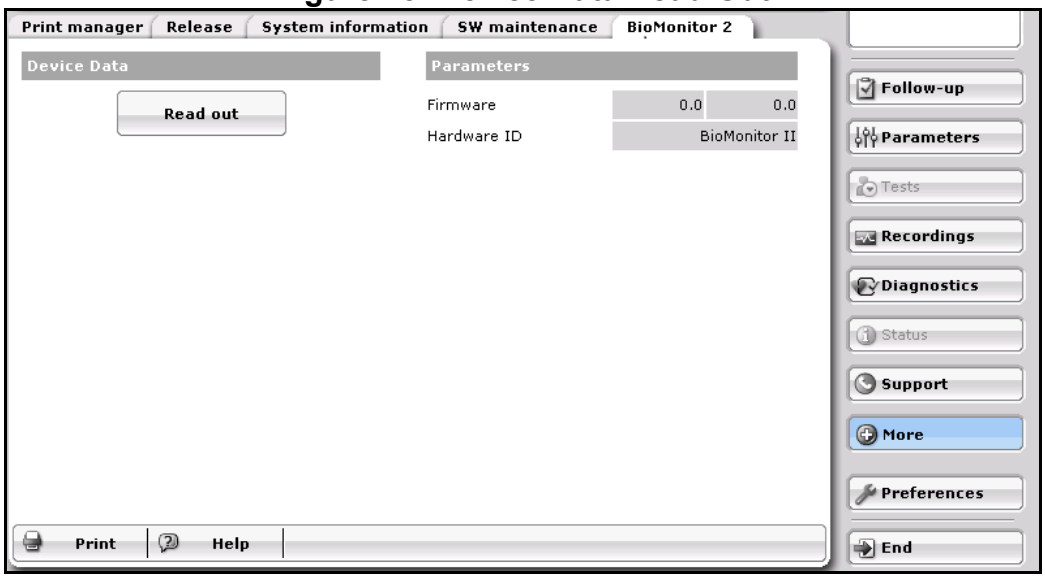
- While in the Noise duration trend with the date of visit selected, print a screenshot by following Figure 12. To do this, connect the USB flash drive (orange arrow) to the Programmer USB port. Open left paper tray (green arrow). Press the Stop and the 10 button (blue arrow).

III. 90-day visit Device Data "Read out"

Please follow these steps at the end of the 90-day visit.

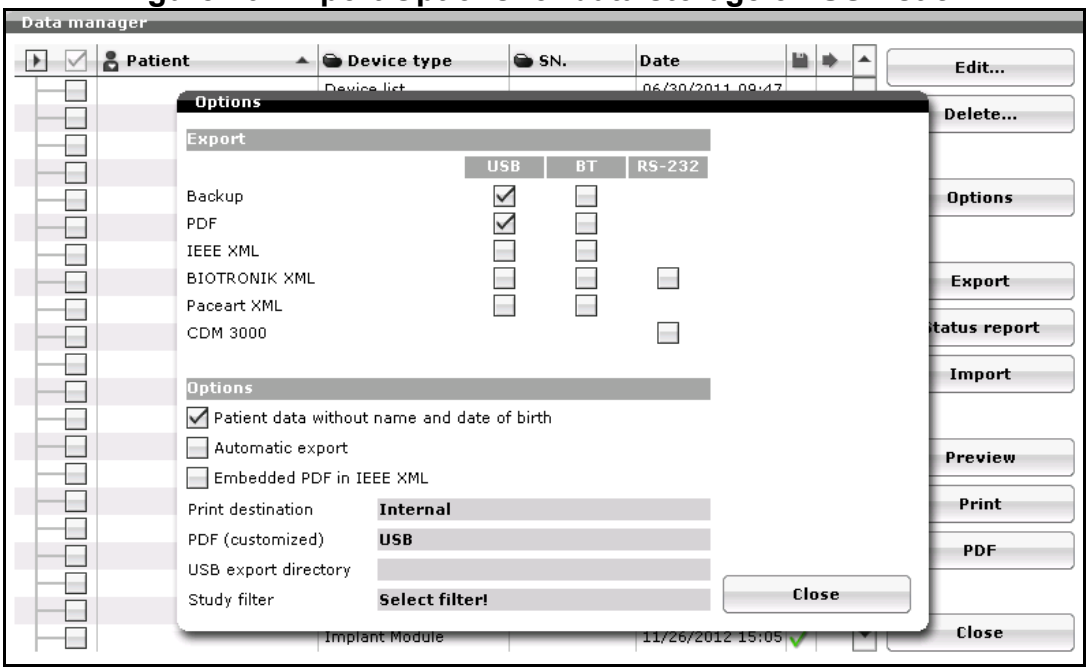
- Connect a USB flash drive to the Programmer
- Apply the programming wand above the BioMonitor 2.
- Download the data from the BioMonitor 2 memory while the subject is in a reclined position. Select "More" → "BioMonitor 2" → "Device Data" → "Read out". The data transmission can take about 5 minutes.

Figure 15: Device Data Read Out



- Open the “Data Manger” and select the correct subject and corresponding visit date.
- Under “Options,” select “Backup” and “PDF” under the USB column as shown in Figure 16. Verify that “Backup” is selected; this is the only way to export the raw data with the follow-up information. Note that the automatic export option is not required.

Figure 16: Export Options for data storage on USB stick



- After closing the “Options” window, open “Preview” and select all follow-up data.
- Close the “Preview” window and select “Export.”