Clinical Protocol

for the

BIO|GUARD-MI Study

BIO monitorinG in patients with preserved left ventricUlar function AfteR Diagnosed Myocardial Infarction

IDE # G180155

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BIOTRONIK, Inc.

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U.S. specific amendment of

BIO|GUARD-MI Study

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PROTOCOL SIGNATURE PAGE

The signature below constitutes the receipt and review of the BIOGUARD MI 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 guidelines.

Principal Investigator:

_____

Name (please print)

_____ _____

Signature Date

Summary

Title	**BIO** monitorin**G** in patients with preserved left ventric**U**lar function **A**fte**R** **D**iagnosed **M**yocardial **I**nfarction
Acronym	BIO|GUARD-MI study
Subject collective	Patients with a myocardial infarction, CHA_2DS_2-VASc Score ≥ 4 in men / ≥ 5 in women and left ventricular ejection fraction > 35%
Design	Prospective, controlled, randomized (1:1), parallel-group, open, multi-center, international study with an event-driven design
Investigational Medical Device(s)	BioMonitor 2 or successor implantable cardiac monitor
Accessory components to Investigational Medical Device	BIOTRONIK Home Monitoring®: CardioMessenger II, IIs or successors; Programmer: Renamic, ICS 3000 or successors with current software version; Accessory device: Remote Assistant if applicable
Primary objective	The primary objective of the BIO|GUARD-MI study is to investigate whether the early diagnosis of cardiac arrhythmias, provided by the BioMonitor in connection with remote monitoring, and the consequent treatment of the subject will decrease the risk to experience a MACE in patients with a history of MI, CHA2DS2-VASc Score ≥ 4 in men / ≥ 5 in women and LVEF > 35%.
Primary endpoint	Time to first MACE
Secondary objective	All-cause mortality and all individual components of the composite primary endpoint will also be evaluated separately. In addition, the occurrence of arrhythmias and related therapies will be evaluated. The life quality will be evaluated using the WHO (Five) Well-Being Index.

Secondary endpoints	**To assess the time to**
	• Death from any cause
	• Cardiovascular death
	• First acute unscheduled hospitalization or urgent visit for worsening of the patient status due to heart failure or first acute unscheduled hospitalization due to adverse events of the following list:
	  • Arrhythmia
	  • Acute coronary syndrome
	  • Stroke
	  • Major bleeding
	  • Systemic embolism
	To assess the time to first
	• Atrial fibrillation
	• Atrial flutter
	• Non-sustained VT
	• Sustained VT
	• Sinus arrest
	• Sinus bradycardia
	• 2nd or 3rd degree AV block or advanced AV block
	To assess the quality of life
	• WHO (Five) Well-Being Index

Further data of interest	To assess in a descriptive manner, the types and number of therapeutic interventions administered after arrhythmias detected by remote monitoring. Utility values for an economic evaluation will be estimated by using the EQ-5D-5L questionnaire.
Sample size	Up to 360 subjects within the United States, up to 2900 subjects worldwide
Study sites	Up to 20 sites within the United States, up to 80 sites worldwide
Inclusion criteria	• Patient has a history of MI according to guidelines • CHA2DS2-VASc Score ≥ 4 in men / ≥ 5 in women • LVEF > 35% as estimated within 6 months before enrollment but after conclusion of AMI treatment • Patient accepts activation of Home Monitoring • Patient is able to understand the nature of the clinical study and has provided written informed consent

Exclusion criteria	• Patients with hemorrhagic diathesis • Permanent oral anticoagulation treatment for atrial fibrillation • Indication for chronic renal dialysis • Pacemaker or ICD implanted or indication for implantation • Parkinson's disease • Life expectancy < 1 year • Participation in another interventional clinical investigation during the course of the study, i.e. the participation in a non-interventional* clinical investigation is allowed • Age < 18 years • Woman who are pregnant or breast feeding
Study duration	The follow-up period of the individual subject is dependent on the time of entry into the study. All study subjects will be followed until the number of needed endpoints for the final analysis is reached or the DSMB determines a premature study termination.

* We define non-interventional clinical investigations as a study where the product(s) under investigation is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the product under investigation is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data.

Follow-up scheme:	**Enrollment/Baseline** • Verification of inclusion/exclusion criteria • Subject information and provision of written informed consent • Randomization (device yes/no) • Demographics and medical history/medical conditions • Specification of MI • NYHA classification • Echocardiographic data • Adverse events • Scheduling implantation of the Implantable Cardiac Monitor and/or discharge **BioMonitor implantation, if applicable** (As soon as possible but at latest 8 weeks after enrollment) • Implantation of the BioMonitor • Programming of the BioMonitor • Adverse events • Final subject instruction on BioMonitor **Discharge** • Final subject instruction on study course • Cardiovascular medication and non-cardiovascular medication • Lab parameters • Adverse events **Follow-up** • No pre-planned in-office follow-up visits • Unplanned visits (subject- or investigator initiated) possible; reason for visit and treatment will be documented • Initial telephone call at 4 weeks post-enrollment • Telephone contact every 6 months using a questionnaire with focus on endpoint-related data as well as questionnaires covering quality of life aspects (WHO-5 Well-being Index and EQ-5D-5L questionnaire) **Termination** • Final subject contact, either via office visit or telephone contact • Documentation whether the study termination was regular or premature and if applicable the reason for a premature termination • Adverse events

Sponsors	BIOTRONIK SE & Co.KG Center for Clinical Research Woermannkehre 1 12359 Berlin, Germany Represented by local sponsor in the U.S.: BIOTRONIK, Inc. Clinical Studies Department 6024 Jean Road Lake Oswego, Oregon 97035
Coordinating Investigator	[redacted]
Boards and Committees	• Central Electrocardiogram Monitoring Board • Data Safety Monitoring Board • Endpoint and Adverse Event Committee • Steering Committee • Publication Steering Committee

1. Introduction

The BIOGUARD MI study aims to investigate whether continuous arrhythmia monitoring and detection, using an ICM (BioMonitor 2 or market released successor, hereafter referred to as BioMonitor) in patients after a myocardial infarction (MI) with LVEF > 35% but with other cardiovascular risk factors, decreases the risk of MACE if patients are appropriately examined and treated for the observed arrhythmias. The population selected for this clinical investigation is expected to have an increased risk of cardiac arrhythmias. It is expected that the BioMonitor will facilitate early diagnosis of cardiac arrhythmias and result in treatment of the arrhythmias or other cardiac conditions that may present, to prevent clinical endpoints and disease progression. This study will enroll up to 2900 subjects at up to 80 clinical study sites worldwide. Up to 360 subjects at 20 study sites are planned within the United States.

Subjects eligible for the study have had an myocardial infarction with a CHA_2DS_2-VASc Score ≥ 4 in men / ≥ 5 in women and left ventricular ejection fraction > 35%. Prior to enrollment, eligible subjects will be identified and will be asked to provide written informed consent. Subjects will be randomized 1:1 to receive a BioMonitor device or standard of care (no BioMonitor device). Post enrollment, subjects will complete a pre-hospital discharge visit, an initial telephone call at 4 weeks, and then continue with telephone contacts every 6 months until the end of the study. A final study termination visit may also be performed.

This clinical study protocol is U.S. specific based on the basic international protocol of the BIOGUARD MI study. The international protocol is applicable for all non-U.S. sites and based on the international standard ISO 14155. The U.S. protocol is applicable for all U.S. sites based on FDA GCP requirements. The U.S. sites are also reporting adverse events in accordance with ISO 14155. The local study sponsor for all U.S. sites is BIOTRONIK, Inc., Lake Oswego, OR, USA. The main sponsor for the study is BIOTRONIK SE & Co. KG, Berlin, Germany.

All scientific aspects of the study design, including devices used, primary endpoints, secondary endpoints, additional data of interest, enrollment/implant/follow-up procedures, inclusion criteria, exclusion criteria, and study specific boards/committees are identical. The BIOGUARD MI study has a single registration with ClinicalTrials.gov (NCT02341534) that covers both U.S. and non-U.S. protocols.

1.1 Background

Myocardial Infarction (MI) is the closure of a coronary vessel. It leads to the irreversible necrosis of heart muscle secondary to prolonged ischemia. According to the appearance in the electrocardiogram (ECG) Myocardial Infarction (MI) can be classified as non-ST segment elevation myocardial infarction (NSTEMI) and ST segment elevation myocardial infarction (STEMI) which generally reflects an acute total coronary occlusion.

Although the treatment of MI has improved over the past decades mainly due to introduction of early reperfusion therapy (lytic or percutaneous coronary intervention), every sixth man and every seventh woman in Europe will die from MI [1;2]. Patients with STEMI have a higher acute risk, however, long-term follow-up showed that death rates were higher among patients with NSTEMI with a two-fold difference at 4 years [1]. An explanation for this may be that NSTEMI patients more frequently present with concomitant cardiovascular risk factors such as hypertension, obesity, diabetes and higher age [3-6] .

After MI, the heart adapts to the permanent damage. A generalized autonomic dysfunction results in enhanced automaticity of the myocardium and conduction system and can lead to complications that include cardiac arrhythmias. The necrosed area acts as a substrate for re-entrant circuits and the ongoing coronary artery disease can cause electrolyte imbalances and hypoxia which further contribute to the development of cardiac arrhythmias. Cardiac arrhythmias may result in orthostatic hypotension, increase myocardial oxygen requirements, and predispose the patient to develop additional malignant ventricular arrhythmias. Since arrhythmias are expected to be frequent in MI survivors and contribute to the poor prognosis, it may be reasonable to monitor and treat them aggressively.

Survivors of MI who have a severely impaired left ventricular ejection fraction (LVEF) are at high risk of dying suddenly due to cardiac arrhythmias[7-10]. CARISMA was the first study to use implantable cardiac monitors (ICMs) for continuous ECG monitoring of cardiac arrhythmias in the post-AMI setting including patients with LVEF ≤ 40% and still represents the only experience in this area[11]. This study documented unexpectedly high incidences of new-onset atrial fibrillation (AF), high degree atrioventricular (AV) block, sinus bradycardia, ventricular tachycardia (VT) and ventricular fibrillation (VF)[12]. In summary, 46% of all patients presented with at least one of the pre-specified cardiac arrhythmias of which 85% were asymptomatic. With a mean follow-up duration of two years, 20% of patients experienced a major adverse cardiac event (MACE) including death or hospitalization due to heart failure, re-infarction and stroke. More than 80% of them were diagnosed with an arrhythmia before the event. Hence, a cardiac arrhythmia was the most powerful predictor of a MACE. The study, however, left it open whether preventive treatment based on ICM detections will decrease the incidence of cardiovascular events in high-risk patients.

The assessed high incidences and prognostic significance of cardiac arrhythmias underline the importance of continuous rhythm monitoring in high risk patients after AMI. ICMs provide a much more detailed picture of the incidence of brady- and tachyarrhythmias than conventional follow-up. In addition, newer ICMs (e.g. BioMonitor) include improved algorithms that allow distinguishing different arrhythmias, and also the diagnosis of AF, compared to earlier devices such as those used in the CARISMA study. A unique feature of the BioMonitor is the implemented BIOTRONIK Home Monitoring® function which allows remote access to the subcutaneous electrocardiogram (sECG) recordings. It has been suggested that remote monitoring significantly increases the efficacy of the ICM [13].

The CARISMA study included patients within severely depressed LVEFs ≤ 40% [11;14]. However, 80-90% of patients surviving MI have a relatively preserved LVEF and are therefore assumed to be at lower risk for MACE and arrhythmias [4;15]. While this group as a whole may have a relatively benign prognosis, this may not be justified in subgroups with additional cardiovascular risk factors, particularly increasing age, hypertension and diabetes. Moreover, reduced LVEF is less frequent after introduction of percutaneous coronary intervention (PCI) and addition of multiple antithrombotic agents after revascularization. In a recent study including 1500 unselected consecutive patients with AMI most of the premature deaths due to cardiovascular cause occurred in the group of patients with relatively preserved LVEF but with other risk factors [14].

Thus, there is a clinical need to identify patients at high risk for MACE and arrhythmias with preserved or only mildly reduced cardiac function but other cardiovascular risk factors in place. The BIO|GUARD-MI study has been planned to address this need. It was therefore crucial to implement a tool for risk stratification beyond LVEF to correctly identify patients at high risk after MI.

Although the $CHADS_2$ score has been designed to estimate the stroke risk in patients with AF, evidence has been provided that the score is highly prognostic as a risk stratification tool for both MACE and arrhythmias in patients with LVEF ≤ 40% after MI [16]. In this population the risk of experiencing a MACE was 8 times higher, and the risk of any arrhythmia was 3.7 times increased in patients with $CHADS_2$ score ≥ 3 compared to $CHADS_2$ score = 0. Also in other populations, the $CHADS_2$ score is connected to the risk of AF [17-19] and bradyarrhythmias [12;20-22]. Moreover, the individual components of the $CHADS_2$ score (congestive heart failure, hypertension, age, diabetes, stroke) have also been found to be independently associated with increased risk of VT/VF [7;23-26] and are all known to be independent risk factors for worse outcome in patients after [27].

In recent years, the CHA_2DS_2-VASc Score has superseded the $CHADS_2$ score for its original purpose of stroke risk estimation in AF patients due to a better performance especially in patients with a low risk. Both scores are based on the same items, with the CHA_2DS_2-VASc Score adding points for age above 75 years, female gender and vascular disease. Although more data are available on the general cardiovascular risk prediction of the older $CHADS_2$ Score, it is justified to assume that the CHA_2DS_2-VASc Score will perform similarly well for the purpose of this study. Because the $CHADS_2$ score is perceived as outdated and inferior by many cardiologists, the CHA_2DS_2-VASc Score will be used as main entry criterion of this study.

Compatible with the conclusions drawn from CARISMA, large randomized controlled trials have firmly established that post-MI patients with LVEF ≤ 35% benefit from the implantation of an ICD, which is reflected in current guidelines [28]. However, patients with a preserved or mildly reduced LVEF (≥ 35%) but with additional cardiovascular risk factors, such as those expressed within the CHA_2DS_2-VASc Score, may be considered at high risk for

experiencing both cardiac arrhythmias and consequent MACE. Nevertheless, scientific studies in this population remain sparse.

2. Investigational Device

2.1 Name of Investigational Device

This study utilizes BIOTRONIK's BioMonitor insertable cardiac monitor. The current model, BioMonitor 2, is BIOTRONIK's second generation and is available in one model within the U.S., the BioMonitor 2-AF. The BioMonitor 2 received FDA clearance on April 11, 2016 (K152995 number).

The BioMonitor 2 is indicated to detect the following cardiac arrhythmias:

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

The BioMonitor 2 is indicated for use in:

- Patients with clinical syndromes or situations at increased risk for cardiac arrhythmias
- Patients who experience transient symptoms that may suggest a cardiac arrhythmia
- The device has not been tested for and is not intended for pediatric use

Although the BioMonitor 2 is legally marketed in the U. S. for arrhythmia detection, BIO|GUARD-MI is an investigational study because the BioMonitor 2 is being evaluated for possible benefit in an alternative population of people with increased risk for cardiac arrhythmias that have previously not been studied.

2.2 System Description

Devices included in the clinical study:

- BioMonitor 2 or FDA cleared successor (Figure 1)

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

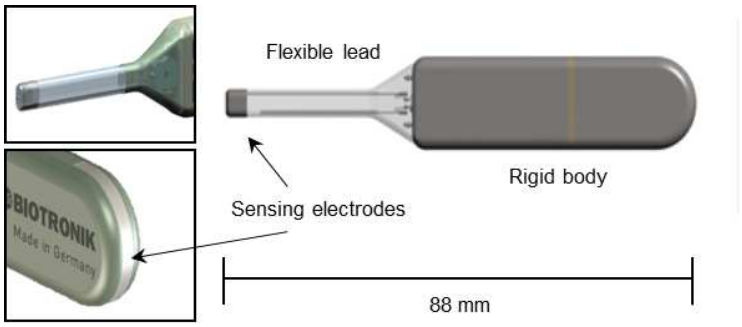
Subjects implanted with a BioMonitor will be monitored with BIOTRONIK's Home Monitoring® system and are therefore provided with the external patient device:

- BIOTRONIK CardioMessenger II, II-S or FDA-cleared successor

Patients who are receiving the investigational device may be provided with a FDA cleared accessory device (Remote Assistant) at the investigator's discretion. The Remote Assistant

allows manual triggering of an ECG recording by the patient and thereby supporting the treating physician in making an accurate diagnosis.

Figure 1: BioMonitor 2



2.3 Description of traceability

Each BioMonitor, CardioMessenger or Remote Assistant has a unique serial number. The traceability is assured by recording the serial number. The information is documented on the corresponding electronic case report form (eCRF) and recorded in the EDC system.

2.4 Description of the investigational device

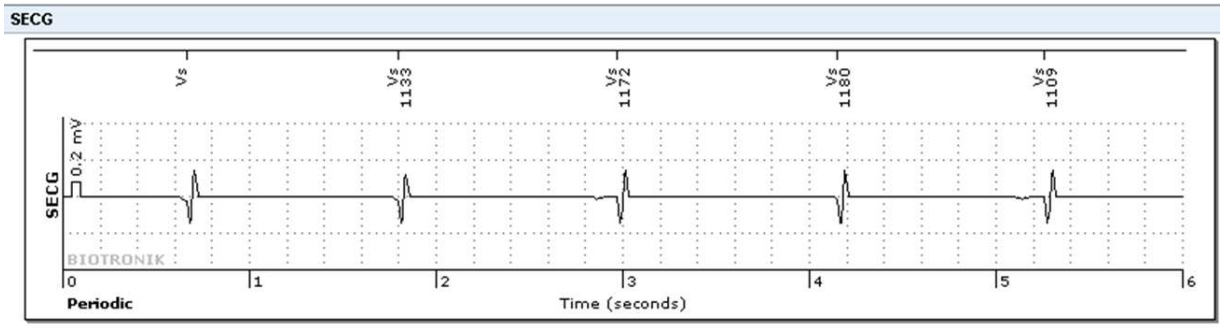
The BioMonitor is a subcutaneous ICM that continuously monitors the heart rhythm. Implantation and follow-up are performed with a portable BIOTRONIK programmer. Additionally, the Home Monitoring feature enables physicians to perform remote diagnosis management over the lifetime of the device. The average service time of the BioMonitor is 4 years according to the technical manual.

The BioMonitor records automatically the occurrence of certain cardiac arrhythmias; these arrhythmias are classified as AF, high ventricular rate (HVR), asystole, sudden rate drop, or bradycardia.

2.4.1 BIOTRONIK Home Monitoring® with daily sECGs

The BIOTRONIK Home Monitoring® system provides early detection of arrhythmic events like high ventricular rates and of silent, asymptomatic events like atrial fibrillation, through the transmission of periodic (Figure 2) and triggered sECG recordings.

Figure 2: Periodic sECG Transmission Example



The BioMonitor 2 has the capability to transmit messages including sECG signals 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. In this study a Central Electrocardiogram Monitoring Board will be installed to ensure a centralized arrhythmia event management process, filtering of false positive events, and consistent alerting of the study sites in case of confirmed events.

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.

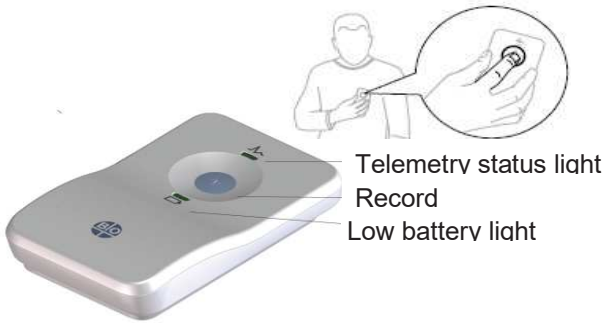
6. Automatic early detection of arrhythmias and device system anomalies by BIOTRONIK Home Monitoring® allows for earlier intervention than conventional in office follow ups.

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.

2.4.2 Remote Assistant for Patient Triggering

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 3, 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 3: Remote Assistant Patient Device



2.5 Summary of training and experience needs

The BioMonitor is a medical implant intended for physicians who are familiar with the implantation of an ICM. The physician must be familiar with the associated risks and complications. The interrogation and programming of the ICM shall only be done by appropriately trained personnel using the BIOTRONIK programmer.

The BioMonitor should be implanted by a physician in accordance with the standard implantation procedures and techniques. Specific information pertaining to procedures is provided in the technical manual of the BioMonitor.

In accordance with the technical manual of the BioMonitor the term ‘insertion procedure’ could be used synonymously to the term ‘implantation procedure’.

3. Justification for the design of the clinical investigation

3.1 Clinical data to support the safety and efficacy of the BioMonitor

3.1.1 The BM01 acute study

The BM01 acute study was an investigational study of the characteristics of the human sECG signals as recorded by the BioMonitor. The purpose of the study was to build a library of sECG signals from members of the targeted patient population and to evaluate algorithm feasibility. The ECG recordings were performed exclusively during the implant procedure of a pacemaker or ICD. After preparation of the tissue pocket, the BM01 device was placed in this pocket. A wand with a sterile cover was positioned on the BM01 device to interrogate ECG signals. The ECG recordings were performed at rest and with patient movements in different device orientations.

The subject pool spanned the range of expected patient ages (41 to 88 years) and body builds (BMI 21 to 42) and included patients who had an ongoing cardiac arrhythmia. The QRS amplitude signal-to-noise ratios were sufficient for QRS detection. The BM01 signal library was used to establish the feasibility of the QRS detection algorithm and the AF detection algorithm.

3.1.2 BioMonitor Master Study

The objective of the Master Study of the BioMonitor was to confirm the safety and efficacy of the BioMonitor to collect post market clinical follow up (PMCF) data. The data of 153 enrolled patients (152 of which received a BioMonitor implant) from 17 clinical sites in 6 countries, including Germany and Denmark, was included within the final report[†].

The patient population was selected according to defined criteria, i.e. patients with suspected cardiac arrhythmia, previous AF diagnosis or AF diagnosis before or after ablation procedure or stroke of unknown origin. The safety of the ICM (primary endpoint 1) was evaluated by the evaluation of the Serious Adverse Device Effect (SADE)-free rate until the 3-month follow-up visit. The efficacy of the ICM (primary endpoint 2) was evaluated by the evaluation of the rate of appropriate QRS detection.

No BioMonitor related SADEs up to the 3 month follow-up were reported. Regarding the efficacy of the BioMonitor, 77 assessments of the QRS-detection performance of the BioMonitor were performed. In 72 cases, the QRS-detection was appropriate which yields in

[†] Master Study of the Implantable Cardiac Monitor BioMonitor, Clinical Investigation Report. June 2, 2015

a rate of 93.5%. Only 5 patients provided a QRS-detection positive predicted value (PPV) smaller than 90% (Min 85.5%).

3.1.3 BIO|MASTER.BioMonitor 2 Study

The objective of the BIO|MASTER.BioMonitor 2 study was to confirm the safety and efficacy of BIOTRONIK's second generation of ICM, the BioMonitor 2, and its respective insertion tool set FIT1 and FIT2. The primary endpoint of the study was to evaluate the device and insertion tool related SADE-free rate through the 3-month follow-up is above 90%. R-wave amplitude at 1-week post implant of the BioMonitor 2 was also compared to the first generation BioMonitor.

A total of 92 patients were enrolled in 13 clinical sites across 4 countries and 90 subjects received a BioMonitor 2 device. A total of 2 SADEs related to the BioMonitor 2 or insertion tools were reported resulting in an SADE-free rate of 97.8% (95% CI, 93.3% to 99.7%), significantly above 90%. The mean R-wave amplitude for the BioMonitor 2 was 0.75 mV at the 1-week follow-up visit. This was significantly higher ($p < 0.001$) than 0.3 mV, the comparison value for the predecessor BioMonitor.

3.1.4 BioInsight Study

The BioInsight study was designed to evaluate the safety and feasibility of performing the BioMonitor 2 insertion procedure in an office setting. All subjects enrolled in the study had an approved indication for continuous arrhythmia monitoring with an ICM and were implanted with a US market released BIOTRONIK BioMonitor 2. The primary objective was to characterize all insertion procedure-related adverse events requiring additional invasive intervention to resolve though the 90-day follow-up. Secondary objectives included characterization of all insertion procedure-related adverse events not included in the primary objective, characterization of the insertion procedure, and characterization of device functionality post-insertion.

Of 82 subjects enrolled at 6 study sites in the U.S., 77 patients underwent an insertion procedure. All insertion procedure attempts were successful. The most common device orientation was position B (parallel to the sternum over the fourth intercostal space), with the device antenna pointing down (toward the feet). Incision size ranged from 8 to 21 mm with a mean of 14.9 mm and the duration of the procedure averaged 8.4 minutes with a range of 3.5 minutes to 30 minutes.

There were no reported adverse events that met the criteria for primary objective 1; therefore, the rate of all insertion procedure-related adverse events that required additional invasive intervention to resolve is 0%, 95% CI: (0.0%, 5.0%). Only two adverse events were reported and both were classified as insertion procedure-related that did not require additional invasive intervention to resolve. The overall event rate for all reported adverse events was 2.7%, 95% CI: (0.3%, 9.5%) and is similar to in-office ICM insertion rates

reported in literature. The average R-wave amplitude was 0.77 ± 0.5 mV at insertion and 0.67 ± 0.3 mV at 90 days. The average noise burden was 2.5 ± 4.64 % at wound check and 2.7 ± 5.79% at 90 days. Daily BIOTRONIK Home Monitoring® transmissions for 76 subjects showed stable R-wave amplitudes and noise burden through the 90-days post-insertion with an overall average of 0.68 mV and 2.7% respectively.

3.2 Clinical data to support the design of the BIO|GUARD-MI study

The BIO|GUARD-MI study aims to investigate whether the risk to experience a MACE in a population with history of MI, with LVEF > 35% and additional cardiovascular risk factors can be decreased by an early detection of cardiac arrhythmias provided by continuous ECG monitoring using an ICM and the consequent treatment of the patient.

The first and only other study to use ICMs for continuous ECG monitoring of cardiac arrhythmias in the post-AMI setting included patients after AMI with LVEF ≤ 40% [11].

The primary objective of the study was to describe the incidence of pre-defined cardiac arrhythmias. Unexpectedly high incidences of new-onset AF, high degree AV block, sinus bradycardia, VT and VF were diagnosed on the ICM during the study [11;12;16]. Moreover, with a mean follow-up duration of two years, 20% of patients experienced a MACE and more than 80% of them were diagnosed with an arrhythmia before the event.

The authors conclude [11]:

- that cardiac arrhythmias were the most powerful predictor of a MACE, and many of them would have remained unnoticed without an ICM
- to initiate comprehensive diagnosis and appropriate therapies after detection of arrhythmias

The clinical relevance of the study is limited because it has been shown that post-MI patients with EF < 35% - and thus the majority of the CARISMA patients - are indicated for an ICD [28;29]. With a LVEF > 35%, the BIO|GUARD-MI population is not indicated for an implantable device and still only little is known about this population which is generally considered at moderate risk compared to patients with lower LVEF. However, compared to healthy subjects, the MACE rate of post-MI patients with preserved or only moderately reduced LVEF is substantial, especially when considering cardiovascular risk factors ($CHADS_2$ score) in addition [30-33].

3.3 Justification of the design

Although the patient population of this study has not been studied directly, clinical data indicate that considerable rates of arrhythmias and MACE must be expected. The population

of subjects meeting the enrollment criteria is large and the study aim to prevent MACE is relevant both for the individual subject and the society.

The benefit of continuous ICM monitoring in patients at high risk for arrhythmias has been shown previously [11]. The value of preventive treatment initiated by detected arrhythmias has not been shown yet but seems plausible and crucial to investigate.

To provide continuous monitoring post-MI, potential subjects will be enrolled, randomized (50% of the subjects will be implanted with the BioMonitor) and implanted as soon as possible, if applicable.

Other than the implantation of the investigational device, which is not part of the clinical routine for the studied patient population, the chronological order and the scope of this study do not interfere with the medical standards at the sites with regards to patient treatment or follow-up care. It is solely up to the treating physician how to guide the patients. No requirements are placed on the therapy and no pre-planned in-office visits are part of the study. However, treatment recommendations for detected arrhythmias compatible with current treatment guidelines will be provided to the investigators within a separate document.

Although the study does not enforce any therapies, certain Home Monitoring messages may lead to subject calls, bringing about additional follow-up visits with intensified diagnostic procedures, and consequently in the initiation of therapy.

To ensure complete reporting of MACE endpoints, all subjects will be contacted directly via telephone at regular intervals every 6 months.

4. Study Design

The BIO|GUARD-MI study is a multicenter, prospective, randomized (1:1), controlled, parallel-group, open, international study with an event-driven design.

The study was divided into two phases. The U.S. sites will be joining the second phase of the study. At the time of submission of the U.S. study protocol the gate to enter the second phase (20 endpoints reached) was estimated by the main sponsor after blinded review of all cardiovascular SAEs. After the Endpoint and Adverse Event Committee (EAEC) has officially adjudicated that 20 subjects have reached an endpoint a statement will be prepared to announce the official start of the second phase of the study.

The second phase is currently planned to last until approximately 2021. As study stop will be announced once the required number of endpoints is reached, the individual time for subject participation depends on time of enrollment of the subject in the study. As U.S. subjects will start in phase 2 of the study, the estimated individual subject study participation duration is between 0 and 35 months. The study includes an enrollment-assessment and randomization procedure. The randomization is 1:1, either in the BioMonitor group (subjects are implanted with the BioMonitor) or in the control group (subjects do not receive a device). The qualifying measurement of the LVEF should be from the time after conclusion of the acute treatment of the most recent MI, but not older than 6 months. For subjects randomized to the BioMonitor group, the implant shall be performed as soon as possible, but no more than 8 weeks after enrollment. Most study procedures will typically take place during the index hospitalization[‡] (enrollment, implantation if applicable and discharge).

Following discharge, subjects will be treated according to clinical routine/guidelines. Hence, no study specific pre-planned procedures will be performed. Subjects should contact their general practitioner (GP) or cardiologist as in standard post-MI care as needed for their care or in the event of any new symptoms.

To assess the primary endpoint, all subjects will receive telephone calls every 6 months and will be interviewed by means of a questionnaire. These phone calls will be conducted in a way as not to interfere in the normal health care, i.e. the subject will receive no medical advice of any kind but will only be asked about events of the preceding period (see section 8.6).

Additionally, subjects who are randomized to the BioMonitor group may be contacted and scheduled for a visit when an arrhythmia was detected by the BioMonitor, if the investigator considers this clinically indicated.

The follow-up period of the individual subject is dependent on the time of entry into the study. All subjects will be followed until the number of needed endpoints for the final

[‡] The term index hospitalization refers to the time of enrollment of the subject at the study site.

analysis is reached or the DSMB determines a premature study termination. Thereafter, the formal study termination is announced and all subjects will receive a final telephone call to inform them about the study end and, if applicable, to schedule the study termination visit.

4.1 Objectives

4.1.1 Primary objectives

The primary objective of the BIO|GUARD-MI study is to investigate whether the early diagnosis of cardiac arrhythmias, provided by the BioMonitor in connection with remote monitoring, and the consequent treatment of the subject will decrease the risk to experience a MACE in subjects with a history of MI, CHA_2DS_2-VASc Score ≥ 4 in men / ≥ 5 in women and LVEF > 35%.

See Section 5.2 for the definition of MACE.

4.1.2 Secondary objective: Arrhythmia detection

It will be investigated if the implantation of the ICM leads to a faster detection of an arrhythmia that requires a guideline-recommended therapy than a strategy of conventional follow-up.

4.1.3 Other secondary objectives

In parallel to the primary objective and the definition of MACE, all individual MACE components will be evaluated separately and compared between the study groups.

- All-cause mortality: The occurrence of death for any cause will be recorded and analysed.
- Cardiovascular death: The occurrence of cardiovascular death will be recorded and analyzed.
- Worsening of the subject status due to heart failure: The occurrence of worsening of the subject status due to heart failure requiring hospitalization or urgent visit will be recorded and analyzed.
- Hospitalization resulting from arrhythmia: The occurrence of hospitalization resulting from arrhythmia will be recorded and analyzed.
- Hospitalization resulting from acute coronary syndrome: The occurrence of hospitalization resulting from acute coronary syndrome will be recorded and analyzed.
- Hospitalization or death resulting from stroke: The occurrence of hospitalization or death resulting from stroke will be recorded and analyzed.

- Major bleeding requiring hospitalization: The occurrence of major bleeding requiring hospitalization will be recorded and analyzed.
- Systemic embolism requiring hospitalization: The occurrence of systemic embolism requiring hospitalization will be recorded and analyzed.
- Arrhythmias: The occurrence of arrhythmias will be recorded and analyzed independently of whether a consequent therapy is indicated.
- Type of initiated therapies: It will be evaluated which diagnoses will be made and which therapies will be initiated, based on ICM-detected arrhythmias.
- Therapies: It will be investigated if the implantation of the ICM leads to a faster detection of an arrhythmia that requires a guideline-recommended therapy than a strategy of conventional follow-up.
- Quality of Life (QoL): The investigation of the subjects' quality of live is not intended to show a benefit by the implantation of the ICM, but to exclude that the implantation or the monitoring of subjects has a negative impact on their well-being.

4.2 Measures taken to minimize or avoid bias

4.2.1 Randomization

A block randomization stratified for center effects and STEMI/NSTEMI is used to minimize any potential bias due to center specific effects and STEMI/NSTEMI.

All subjects included are assumed to be at increased risk for MACE. However, currently it is unknown which subjects benefit particularly from the study treatment. Thus, no other strata are implemented in the randomization procedure.

Due to the large sample size, other unbalanced confounding factors are expected to be of low relevance.

For subjects of the BioMonitor group and Control group, the randomization date is defined as the discharge from the index hospitalization.

4.2.2 Blinding

The investigator can't be blinded because diagnostic information from the ICM has to be used. The blinding of the subject is not possible due to the invasive procedure depending on the randomization result. All measures will be taken to assure the blinding of the EAEC. These measures will be explicitly documented in a separate manual.

4.2.3 Other

Several methods to reduce bias are implemented in this study, including, but not limited to:

- Potential subject selection according to pre-defined inclusion and exclusion criteria.
- It is the intention of the study design that all subjects will be followed-up and treated in accordance with clinical routine/guidelines. Nevertheless, to gather endpoint information all subjects will be contacted via telephone every 6 months.
- In case of Home Monitoring findings, subjects in the BioMonitor group may have more contacts to the study site, and thus a potentially more complete reporting of endpoints. Nevertheless, the frequency of telephone follow-up calls in both cohorts should remain equal and independent of Home Monitoring findings. Thus, the contract research organization (CRO) in charge of performing the telephone contacts will remain blinded to information received from other contacts. As a quantitative measure for over-reporting, a separate analysis will be conducted involving only primary endpoints reported by subjects during the telephone calls.
- Standardized procedures/processes for:
    - Standardized telephone procedures outlined in a separate telephone manual
    - Standardized methods for data collection, including the documentation of potential confounding factors, such as subject demographics, medical history and procedural parameters
    - Standardized procedures for BioMonitor implantation in accordance with the technical manual
- Formation of a Publication Steering Committee.
- Formation of an Endpoint and Adverse Event Committee (EAEC) that will assess all cardiovascular SAEs and all cases of subject death in a blinded and standardized manner regarding the primary endpoint.
- A CEMB will be formed to ensure a standardized interpretation of the Home Monitoring findings and consequent forwarding to the study sites.

5. Study Endpoints and Hypotheses

5.1 Primary hypotheses

For assessing the primary endpoints, Kaplan-Meier curves will be constructed for the time to first MACE for both study groups according to the intention-to-treat principle. The hazard ratio is defined as the rate of the BioMonitor group divided by the rate of the control group.

The following set of hypotheses (null hypothesis H_0 and alternative hypothesis H_A) will be tested.

H_0: Null hypothesis: $H_0 : HR \geq 1$

which means that monitoring subjects of the BioMonitor group will *not* lead to a long time-to-first-event of MACE compared to the control group.

H_A: Alternative hypothesis: $H_A : HR < 1$

which means that monitoring subjects of the BioMonitor group will lead to a long time-to-first-event of MACE compared to the control group.

It is expected that there is a HR < 1 in favor of the BioMonitor group. A rejection of the null hypothesis indicates that the BioMonitor group has a statistically significant longer time to first MACE event compared to the control group.

5.2 Primary endpoint

The primary endpoint is the time from randomization to the first MACE during the clinical investigation. Subjects without MACE are censored, i.e. the time from randomization until the earliest date of drop-out, study termination, or date of freezing the Clinical Data Management System database (in case of interim analyses) is considered. Subjects who reach the primary endpoint will continue to be followed up until the formal termination of the study is announced.

A major adverse cardiac event (MACE) comprises the following events:

- Cardiovascular death
- Worsening of the patient status due to heart failure, requiring acute unscheduled hospitalization or urgent visit

or acute unscheduled hospitalization due to adverse events (AE) of the following list:

- Arrhythmia
- Acute coronary syndrome
- Stroke
- Major bleeding

- Systemic embolism

5.2.1 Endpoint assessment definitions

A further specification of the endpoint adjudication process will be given by the experts of the Endpoint and Adverse Event Committee (EAEC) within a separate charter.

Rationale:

The patient population enrolled in the BIO|GUARD-MI study is expected to be at higher risk for clinical events and cardiac arrhythmias compared to the general population. Arrhythmias are connected to clinical events. All components of this composite primary endpoint are relevant clinical events and can occur in the context of arrhythmias.

BIO|GUARD-MI aims to investigate if cardiac monitoring of arrhythmias by the BioMonitor, and the consecutive treatment, is beneficial with respect to a reduction of clinical events (MACE).

Measurement:

Information about the primary endpoint will be obtained from the Adverse Event reporting of the study. Adverse events will be actively addressed by contacting all subjects directly via telephone every 6 months and completion of a standardized questionnaire. The telephone follow-up will be performed by an experienced CRO similarly in charge of tracking the respective source data. All resulting AEs will be brought immediately to the attention of the responsible investigator for evaluation and to assure that the reporting timelines are met. In addition, all cardiovascular SAEs and cases of subject death will be evaluated by a blinded central EAEC and assessed with respect to the definition of the primary endpoint.

5.3 Secondary hypotheses

The objective to show that arrhythmias requiring guideline-recommended therapy will be detected earlier in the BioMonitor group will be formally tested similarly to the primary hypothesis. The HR is defined as the rate of the BioMonitor group divided by the rate of the control group.

H_0: Null hypothesis: $H_0 : HR \leq 1$

which means that monitoring subjects of the BioMonitor group will *not* lead to shorter time to first arrhythmia that requires guideline-recommended therapy, in th BioMonitor group compared to the control group.

H_A: Alternative hypothesis: $H_A : HR > 1$

which means that monitoring subjects of the BioMonitor group will lead to a shorte time to first arrhythmia that requires guideline-recommended therapy compared t the control group.

It is expected that there is a HR > 1 for the BioMonitor group. A rejection of the null hypothesis indicates that arrhythmias are detected earlier in the BioMonitor group.

No hypotheses have been pre-defined for the other secondary objectives. Details will be specified in a separate Statistical Analysis Plan (SAP).

5.4 Secondary Endpoints

5.4.1 Secondary endpoint: Time to first arrhythmia detection

This secondary endpoint comprises the time from randomization to the detection of an arrhythmia that requires guideline-recommended therapy. Subjects without arrhythmia detection are censored, i.e. the time from randomization until the earliest date of drop-out, study termination, or date of freezing the Clinical Data Management System database (in case of interim analyses) is considered.

Rationale:

BIO|GUARD-MI aims to investigate if cardiac monitoring of arrhythmias by the BioMonitor is effective.

Measurement:

Information about the secondary endpoint will be obtained from the Adverse Event reporting of the study as described for the primary endpoint. Furthermore arrhythmias and related therapies resulting from BioMonitor information will be recorded on the respective eCRFs.

5.4.2 Other secondary endpoints

All-cause mortality will be analyzed as a secondary endpoint.

Further, in parallel to the primary endpoint and the definition of MACE, all individual MACE components will be evaluated separately and compared between the study groups. It is well recognized that, due to the lower numbers of these events, the study is not powered for confirmatory hypotheses testing. Thus, no secondary hypotheses have been put forward.

Rationale:

Since the primary endpoint is a composite comprising several clinical events of different relevance, it is of interest to analyze the data of each event separately.

Furthermore, information will be obtained regarding relevant cardiac arrhythmias.

The combination of information about arrhythmias and clinical events will allow drawing conclusions regarding the interrelation of arrhythmias and clinical endpoints. It may be of

relevance for the risk prediction in these subjects and may allow developing treatment options.

Measurement:

All relevant arrhythmias will be documented by the BioMonitor and consequently transmitted via BIOTRONIK Home Monitoring® to the responsible investigator for assessment.

5.4.2.1 Time to death from any cause or heart transplantation

Assessment of the time from randomization to death for any reason or heart transplantation during the clinical investigation.

5.4.2.2 Time to cardiovascular death or heart transplantation

Assessment of the time from randomization to cardiovascular death or heart transplantation during the clinical investigation. A specified endpoint definition will be given by the members of the EAEC and documented in a separate charter agreement.

5.4.2.3 Time to first worsening of the patient status due to heart failure requiring hospitalization or urgent visit

Assessment of the time from randomization to first hospitalization or urgent visit for worsening of the subject status due to heart failure, or death due to heart failure. A specified endpoint definition will be given by the members of the EAEC and documented in the charter agreement.

5.4.2.4 Time to first hospitalization resulting from an arrhythmia

Assessment of the time from randomization to the first hospitalization resulting from an arrhythmia or death resulting from arrhythmia. A specified endpoint definition will be given by the members of the EAEC and documented in the charter agreement.

5.4.2.5 Time to first hospitalization resulting from acute coronary syndrome

Assessment of the time from randomization to the first hospitalization resulting from acute coronary syndrome or death resulting from acute coronary syndrome. A specified endpoint definition will be given by the members of the EAEC and documented in the charter agreement.

5.4.2.6 Time to first hospitalization resulting from stroke

Assessment of the time from randomization to the first hospitalization resulting from stroke or death resulting from stroke. A specified endpoint definition will be given by the members of the EAEC and documented in the charter agreement.

5.4.2.7 Time to first hospitalization resulting from major bleeding

Assessment of the time from randomization to the first hospitalization resulting from major bleeding or death resulting from major bleeding. A specified endpoint definition will be given by the members of the EAEC and documented in the charter agreement.

5.4.2.8 Time to first hospitalization resulting from systemic embolism

Assessment of the time from randomization to the first hospitalization resulting from systemic embolism or death resulting from systemic embolism. A specified endpoint definition will be given by the members of the EAEC and documented in the charter agreement.

5.4.2.9 Time to first arrhythmia

Assessment of the time from randomization to first arrhythmia.

5.4.2.10 Type of initiated therapies

Evaluation of the diagnoses and consequent type of therapies based on ICM-detected arrhythmias.

5.4.2.11 Time to first therapy

Assessment of the time from randomization to first therapy. In this context therapy is the attempted remediation of the subject's regular heartbeat. To ensure a standardized proceeding, guideline-based therapy recommendations will be provided to the participating investigators within a separate manual.

5.4.2.12 Quality of Life (QoL)

A further secondary endpoint is the assessment of the subject's quality of life. The subject's quality of life will be recorded during the regular telephone contacts using the WHO-5 Well-being Index.

5.5 Further data of interest

Home Monitoring data of BioMonitor patients provide statistically processed information about further diagnostic or technical data. These data will be analyzed in an explorative manner by the sponsor to get hints and information about possible trends.

In addition, the EQ-5D-5L questionnaire will be administered during the telephone contacts to estimate utility values at different time points for an economic evaluation.

6. Statistical considerations

6.1 Statistical design, method and analytical procedures

The study was statistically designed to allow for early discontinuation in case of superiority and to adapt the sample size in case of positive results but insufficient power to meet the statistical significance with the initially planned sample size.

6.1.1 Group sequential design

The study is designed as a three-stage adaptive group sequential test procedure according to O'Brian Fleming with survival endpoint, where the inverse normal method is used to combine the separate stage information [42].

6.1.2 Full Analysis set based on the ITT principle

The analysis of the primary hypothesis is performed on the full analysis set based on the intention-to treat (ITT) principle; i.e. the set of data from all randomized subjects by minimal and justified elimination of subjects. This set is used to estimate the effect of the experimental intervention with greatest external validity. Subjects allocated to a randomization group are analyzed as members of that group irrespective of their compliance to the planned course of treatment, e.g. cross-over to the other group.

The ICH-E9 guideline states that "there are a limited number of circumstances that might lead to excluding randomized subjects from the full analysis set including … the failure to take at least one dose of trial medication and the lack of any data post randomization."

In accordance to this guideline, the following subjects will be excluded from the analysis set

- Subjects of the BioMonitor group and control group in case of a drop-out before discharge from the index hospitalization
- Subjects without signed informed consent form

6.1.3 Per-Protocol Analysis Set

A supportive analysis of the primary hypothesis is performed on the per-protocol set (efficacy sample), which is a subset of the subjects from the above full analysis set who complied sufficiently with the protocol. This set is used to ensure that the data would be likely to exhibit the effects of treatment according to the underlying scientific model.

The Per-Protocol Analysis Set is the subgroup of the Full Analysis set after exclusion of

- Subjects with violation of inclusion or exclusion criteria at enrollment

- Subjects with major deviations/violations from the protocol in accordance with the definition given in section 14.2.1
- Subjects of the BioMonitor group without implanted device or drop-out less than 1 month after implantation
- Subjects of the control group in case of a drop-out less than 1 month after index hospitalization

Time-to-first-event data are censored after occurrence of

- Cross-overs from the BioMonitor group to the control group or vice versa
- Major protocol deviations/violations as defined in section 14.2.1

Primary endpoints are not taken into account in the BioMonitor group and in the control group until 1 month after discharge from the index hospitalization.

6.1.4 Statistical methods

Descriptive analyses: The data are presented using descriptive statistical methods. For metric data sets, the mean values, standard deviation, median, maximum and minimum are stated, if appropriate. Ordinal data are described by the median and interquartile range. For nominal data, absolute numbers and relative frequencies are determined.

Inferential analysis of the primary hypothesis: The inverse normal combination test is used to combine the independent increment to a global test statistic. A one-sided logrank test is performed in the context of a confirmatory analysis of the primary hypothesis at every interim and the final analysis.

Explorative multivariable analyses are performed (after the termination of the study, i.e. not after interim analysis) based on the Cox regression model.

Inferential analysis: For the inferential analysis of metric, normal–distributed data, a t-test for interindividual of independent groups or a paired t-test for the intraindividual comparison of paired data is performed. In case the normality assumption of the data is either a priori not justified as specified in the SAP or overtly violated (i.e. by a significant Kolmogorov-Smirnov-Lilliefors or Shapiro-Wilk test result) a non-parametric Wilcoxon-Mann-Whitney rank-sum test or a Wilcoxon-signed-rank test is performed, respectively. For the analysis of relative frequencies, Fisher's exact test is used.

6.2 Sample size

It is expected that there will be p_C^{1year} = 5% subjects with at least one MACE per year in the control group and p_{BioM}^{1year} = 3.75% subjects with at least one MACE per year in the BioMonitor group, which results in a Hazard Ratio = 0.7452 in favour of the BioMonitor.

According to the approximation of Schoenfeld [43] 363 events are needed. However, there is a slight increase of the sample size due to the group-sequential design of O'Brien Fleming. The interim analyses and the final analysis should be conducted with 124, 248, and 372 subjects with at least one MACE during the clinical investigation, respectively.

In total, up to 2900 subjects may be enrolled. The subject number of up to 2900 is based on an expected endpoint-rate of 5%/3.75% per subject year required to reach the study goal of 372 endpoint events. The subject number will be automatically adjusted in the event the endpoint rate deviates from the expected rate. All subjects will be followed until the end of the clinical investigation. The study duration will be approximately 3 years, but ultimately study closure is dependent on when the number of needed endpoints for the final analysis is reached.

This accounts also for loss of information due to drop-outs which remain in the analysis set. According to the adaptive group-sequential design, the sample size can also be adjusted after the first or second interim analysis based on the recommendations of the DSMB. However, the sponsor must confirm any sample size increase and has the right to refuse it.

There is no adjustment of the significance value for stopping for futility.

6.3 Level of significance and the power of the study

The global significance level is of the 1-sided hypothesis is 2.5%. The significance level of the interim analyses and final analysis is given by the O'Brien Fleming method: $\alpha_{interim1}$ = 0.00025, $\alpha_{interim2}$ = 0.007, and α_{final} = 0.0225 [44].

The statistical power of the final analysis is 80%.

6.4 Expected drop-out rate

A drop-out of 5% of the subjects per year is expected. Thereby the limited number of subjects to be excluded from the analysis set is not considered.

6.5 Replacement of subjects

The sample size was calculated under consideration of a certain number of drop-outs. Therefore it is not planned to replace subjects.

6.6 Pass/fail criteria

The pass criteria are to accept the primary alternative hypothesis based on the full analysis set.

6.7 Provision for an interim analysis

There are two interim analyses based on 1/3 and 2/3 of the total number of subjects with at least one MACE.

6.8 Termination criteria

The sponsor may decide to discontinue the study due to organizational reasons based on the observed event rates and the general feasibility of the study. Based on the recommendations of the DSMB for the study after the first and second interim analysis, the study will be stopped for futility when there is a low chance for rejection of the Alternative hypothesis at the final analysis or the need for an increase of the sample size, which is refused by the sponsor.

Stopping for superiority is achieved in case the 1-sided p-value at the interim analyses is below the O'Brien Fleming significance values $\alpha_{interim1}$ = 0.00025 and $\alpha_{interim2}$ = 0.007, respectively.

6.9 Procedures for reporting of deviations to the statistical plan

Deviation(s) from the statistical plan described here are reported via amendments to the protocol and/or via a separate SAP.

6.10 Specification of subgroups

Subgroups are predefined for exploratory analyses with respect to

- the occurrence of the predefined arrhythmias, and to
- the primary endpoint and other predefined outcomes.

The following subgroups are predefined according to their presentation at enrollment:

- All individual components of the $CHADS_2$ score except the age-variable
- Age < median vs. ≥ median
- "Early enrollment" within 40 days of most recent MI vs. "late enrollment" after more than 40 days
- Men vs. women
- CHA_2DS_2-VASc score ≤ 4 in men / ≤ 5 in women vs. ≥ 5 in men / ≥ 6 in women
- LVEF < median vs. ≥ median
- BMI: < 30 vs. BMI ≥ 30
- History of AF yes vs. no

- NSTEMI vs. STEMI
- History or presence of kidney failure yes vs. no

6.11 Procedure for accounting of all data for analysis

Data to be analyzed by descriptive and inferential statistical methods are entered in a Clinical Data Management System by the investigators via the EDC system "iMedNet" (MedNet Solutions, Inc. USA).

Data exports from the Clinical Data Management System and the BIOTRONIK Clinical Data Warehouse with Home Monitoring data will be analyzed with common statistical software packages, e.g. SAS Version 9.3 or IBM SPSS Version 21 for Windows or higher.

6.12 Handling of missing, unused and spurious data

Missing data: With respect to the primary hypothesis, drop-outs are considered as censored data and must not be imputed.

Unused data: Data not needed for pre-specified inferential analyzes are minimized and limited to baseline information which can be obtained without any additional burden for the subject. Such data could be used for descriptive and exploratory analyses.

Spurious data are clarified via the query management, i.e. corrected after approval of an investigator. Outliers are identified during the blind review of the data. In case of a clear evidence of a measurement error, the SAP will be updated before breaking the blind in order to avoid any bias.

6.13 Exclusion of data from confirmatory data analysis

Details with regards to the exclusion of data from confirmatory data analysis are provided in section 6.1.2.

6.14 Minimum and maximum number of subjects per site

Investigation sites are selected with the potential to enroll a minimum number of 40 subjects per year.

Every investigator is free to enroll as many subjects as desired until the sample size for the entire study has been reached and the subject recruitment is ended. Due to the large sample size of the clinical investigation, no bias is expected.

7. Protocol Requirements

7.1 Subject Population

The investigator is responsible for screening all potential subjects and selecting those who are appropriate for study inclusion. The patients selected for participation should be from the investigator's general patient population according to the inclusion and exclusion criteria.

Every investigator can enroll as many subjects as desired until the sample size for the entire study has been reached.

Potential subjects meeting the inclusion criteria and none of the exclusion criteria may be enrolled in the study. According to the sample size calculation (see section 6.2), up to 2900 subjects will be enrolled into the study including 5% drop-outs per year. Thereby the limited number of subjects to be excluded from the analysis set (see section 6.1.2) is not considered.

The enrolled subjects will be randomized in a 1:1 relation to the following study groups:

- BioMonitor group (standard of care and implanted with BioMonitor)
- Control group (standard of care)

Vulnerable persons (by the investigator’s judgment) will be excluded from participation. Examples for vulnerability include, but are not limited to: an age below 18 years, limited contractual capacity, and inability to understand written informed consent. Patients who require a legally authorized representative will not be allowed in the study.

7.1.1 Indications

The BioMonitor 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

7.1.2 Contraindications

There are no known contraindications for the BioMonitor. However, the particular patient’s state of health may determine whether a subcutaneous device will be tolerated long term.

7.1.3 Inclusion Criteria

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

- Patient has a history of MI according to guidelines
- CHA_2DS_2-VASc Score ≥ 4 in men / ≥ 5 in women (see section 7.1.3.1)
- LVEF > 35% as estimated within 6 months before enrollment but after conclusion of AMI treatment
- Patient accepts activation of Home Monitoring
- Patient is able to understand the nature of the clinical study and has provided written informed consent

7.1.3.1 Definition of CHA2DS2-VASc Score

CHA_2DS_2-VASc acronym[§]	**Score**
Congestive heart failure • Signs/symptoms of heart failure or objective evidence of reduced left-ventricular ejection fraction	+1
Hypertension • Resting blood pressure >140/90 mmHg on at least two occasions or current antihypertensive treatment	+1
Age 75 years or older	+2
Diabetes mellitus • Fasting glucose >125 mg/dL (7 mmol/L) or treatment with oral hypoglycaemic agent and/or insulin	+1
Previous stroke, transient ischaemic attack, or thromboembolism	+2
Vascular disease • Previous myocardial infarction, peripheral artery disease, or aortic plaque	+1
Age 65–74 years	+1
Sex category (female)	+1

7.1.4 Exclusion Criteria

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

[§] 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS, (European Heart Journal, doi:10.1093/eurheartj/ehw210))

[*] Hemorrhagic diathesis is defined as an increased susceptibility to bleeding due to a coagulation defect, which can be genetic (e.g., Haemophilia, Glanzmann disease, von Willebrand disease) or acquired (e.g., scurvy, vitamin-K deficiency, leukaemia).

- Patients with hemorrhagic diathesis*
- Permanent oral anticoagulation treatment for atrial fibrillation
- Indication for chronic renal dialysis
- Pacemaker or ICD implanted or indication for implantation
- Parkinson's disease
- Life expectancy < 1 year
- Participation in another interventional clinical investigation during the course of the study, i.e. the participation in a non-interventional** clinical investigation is allowed.
- Age < 18 years
- Woman who are pregnant or breast feeding

7.2 Electronic CRFs and Forms

All parameters and measurements that are recorded within the study are described in this section and are documented on the following eCRFs and forms. Table 1 provides an overview of eCRFs and procedures.

Data collected during subject enrollment, phone contact and termination

- Enrollment eCRF
- Baseline eCRF
- Implantation eCRF
- Discharge eCRF
- Study termination eCRF
- Elective Replacement Indicator (ERI) eCRF
- Remote Assistant eCRF

Data collected due to adverse events (AE)

- Adverse event eCRF
- Concomitant medication log eCRF, required only if AE is suspected to be due to a medication

** We define non-interventional clinical investigations as a study where the product(s) under investigation is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the product under investigation is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data.

- Device deficiency (DD) eCRF

Data collected by the CRO performing the telephone contact

- Telephone follow-up questionnaire
- Quality of life questionnaires

Data resulting from Home Monitoring messages and other medical events requiring additional medical care

- Arrhythmia notification eCRF
- General notification eCRF
- IHF event notification eCRF

Any deviations or violations from the protocol

- Protocol non-compliance (PNC) eCRF

Table 1: Overview eCRFs and Procedures

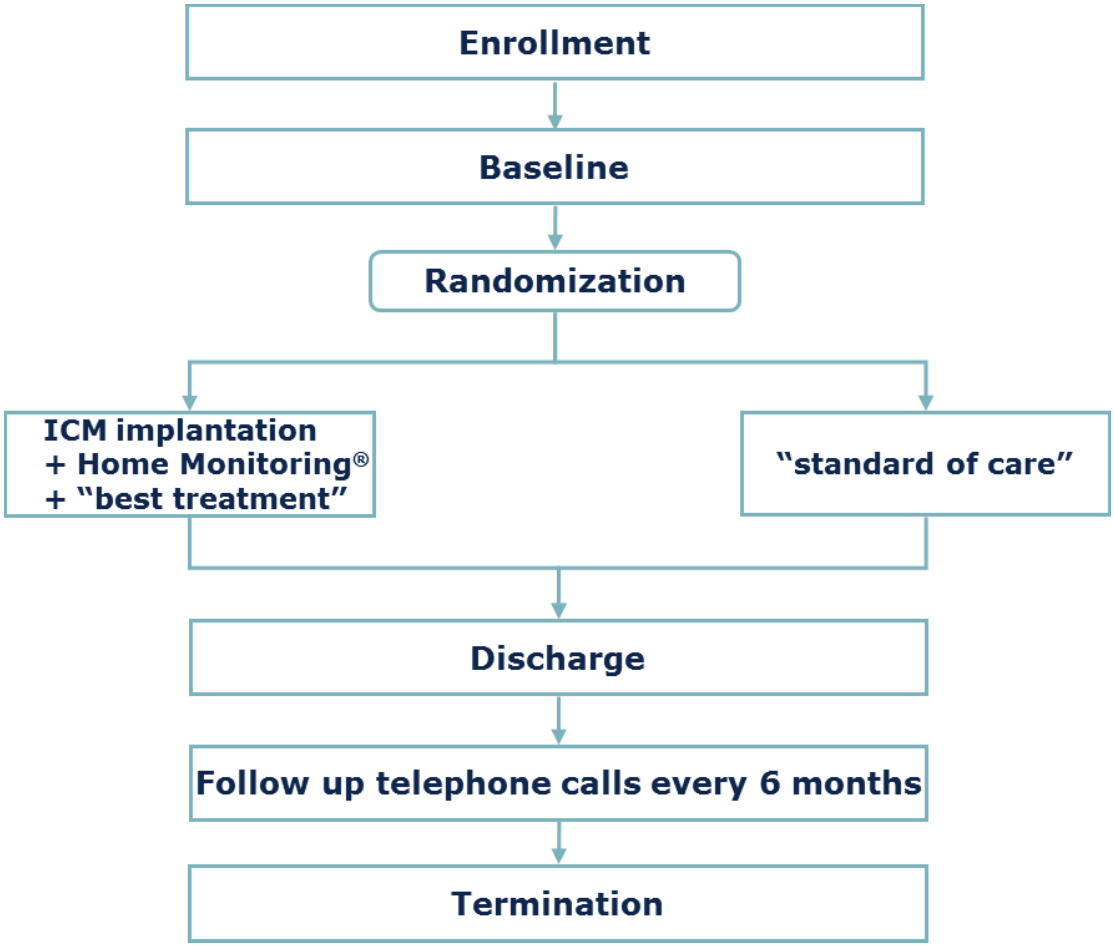
Procedures	Enrollment	Baseline	Implantation	Discharge	Telephone contacts (every 6 months)	Arrhythmia notification eCRF	General notification eCRF	IHF notification eCRF	Termination
Subject informed consent	x								
Verification of inclusion- and exclusion criteria	x								
Subject demographics		x							
NYHA class		x							
Echo parameters		x							
Specification of MI	x								
Medical history/Co-morbidities		x							
Cardiovascular medication				x					
Lab parameters				x					
Randomization result		x							
BioMonitor implantation			x						
BioMonitor interrogation			x						
BioMonitor programming			x						
Adverse events		x	x	x	x	x	x	x	x
Arrhythmia classification						x			
Evaluation of necessity to contact subject						x	x	x	
Subject interview						x	x	x	
Evaluation of necessity of diagnostic procedure						x	x	x	
Telephone follow-up questionnaire					x				
Quality of life questionnaires					x				
Documentation of: - reason for visit - performed examinations, therapies, modifications						x	x	x	
Documentation of: - regular or premature termination - reason for premature termination									x

8. Study procedures

Subjects who have successfully been enrolled in the study will be evaluated at discharge, phone calls every 6 months and a termination visit.

Table 2 provides an overview of the clinical study design. Details of subject eligibility requirements are noted in section 7.1. Details of other specific study procedures and collected data are noted in sections 8.1 to 8.8.

Table 2: Study Flowchart



8.1 Enrollment and Randomization

Prior to enrollment into the clinical investigation, all potential subjects will be evaluated by their physician with regards to the inclusion and exclusion criteria. If these criteria are fulfilled, written informed consent must be obtained from the potential subject prior to enrollment. A subject is considered enrolled upon signing the Informed Consent Form. The

consent process should be documented within the subject's medical record. The Enrollment eCRF will document confirmation that subject has provided written informed consent, verification that inclusion/exclusion criteria were met, specifics related to the subject's history of MI, and confirmation LVEF was greater than 35% within the 6 months prior to enrollment, but after the conclusion of AMI treatment.

All successfully enrolled subjects will be randomized in a 1:1 fashion to the BioMonitor group or the Control group in accordance with the randomization procedure as outlined in section 4.2.1. The randomization code will be generated by the electronic data capture (EDC) system.

8.2 Baseline

The Baseline information collection may occur the same day as Enrollment or it may be delayed from the Enrollment visit, due to the scheduled date of the BioMonitor 2 implant. The following information will be documented in the Baseline Form:

- Result of the randomization
- Demographic information (age, gender, weight, height)
- Echocardiographical data, including LVEF measurement, left atrial volume and left ventricular volume
- NYHA class, (collection of the most current NYHA class post-MI but within 6 months before enrollment, if subject has a history of chronic heart failure)
- Medical history and medical conditions, including cardiac history and TIA/Stroke history
- Occurrence of AEs after written informed consent has been provided

8.3 Implantation

In subjects randomized to the BioMonitor group, the BioMonitor will be implanted after enrollment according to standard procedures as described in the technical manual. See section 2.6 for the summary of training and experience needs.

The implantation of the BioMonitor should be performed according to standard procedures as described in the technical manual. The following information will be documented in the Implantation Form:

- Serial number and product ID (PID) of the BioMonitor
- Initial implant or exchange
- Interrogation and programming details

- Home Monitoring (verification that CardioMessenger was handed out to the subject and turned "on", plus documentation of serial number, general patient instruction on the use of the CardioMessenger)
- Occurrence of AEs since baseline (Any AEs will be collected on a separate eCRF)

8.3.1 Mandatory programming

Arrhythmia detection programming

The investigator is obligated to switch ON all arrhythmias. Hence, the BioMonitor is activated to automatically record the occurrence of AF, HVR, asystole, and bradycardia.

Specified programming recommendations will be provided to the participating investigators within a separate document. However, ultimately the adjustment of the specific arrhythmia detection settings is left with the discretion of the investigator.

Home Monitoring programming

The investigator is obligated to active the Home Monitoring feature. Hence, it is assured that Home Monitoring is set for all detection types.

Patients randomized to the BioMonitor group are educated about how to use the Cardio Messenger. The recommended settings for the HMSC will be specified within the CEMB charter.

8.4 Discharge

Upon discharge from the index hospitalization[††], the subject should receive guideline recommended prescriptions and education about life-style recommendations according to standard of care. In addition, general study aspects such as the telephone follow-up concept should be repeatedly explained to the subject and how to seek medical attention per standard of care. The subjects will be given an information card with a notice indicating that he/she is taking part in a study and that the investigator should be contacted by medical professional personnel in case of any significant medical event. In addition, subjects in both study arms should be reminded to report the details of any hospitalizations and other adverse events. Discharge also includes the documentation of cardiovascular and non-cardiovascular medication and the documentation of general lab parameters (no study specific examination).

- The Troponin value collected should be the highest recorded value related to the most recent MI, if available

[††] The term index hospitalization refers to the time of enrollment of the patient at the investigational site.

- For other lab parameters the most currently estimated value should be collected (not older than 2 months before data of discharge)

8.5 Home Monitoring Analysis and In-Office Visits

No pre-planned, study specific in-office follow-up visits will be performed in this study. Nevertheless event triggered, unplanned in-office visits are expected as a result of arrhythmia detections by the BioMonitor. The following process will be installed to ensure coherent documentation.

Home Monitoring data shall be analyzed on all working days by the CEMB (see section 12.4). If an arrhythmia was detected, the CEMB shall contact the investigator immediately. Contact includes an initial email to the investigator followed by email reminders and a telephone call, if necessary. Parallel to informing the physician, the detected event shall be entered by the CEMB in the EDC system using the 'Arrhythmia notification eCRF (ANF)'. A detailed description of the CEMB-responsibilities and the respective process will be documented in a charter.

After evaluating the event in the Home Monitoring Service Center, the investigator shall enter the assumed rhythm in the EDC system using the same ANF eCRF that was initially applied by the CEMB. Moreover, the timely assessment of the arrhythmia by the investigator will be tracked. Based on the evaluation of the detected event, the investigator decides whether to contact the subject or not. Specifics about the contact and possibly resulting in-office visit shall be recorded in the ANF eCRF and in the adverse event form if applicable. Therefore, event triggered in-office visits and consequently performed examinations/therapies can be attributed to the originating arrhythmia detected by the BioMonitor. To assure an optimal intervention in case of detected arrhythmias, guideline based recommendations will be provided to the participating investigators within a separate document.

In addition to event triggered in-office visits, the subject may be referred by a primary or secondary care provider or the subject may appear at the site on his/her own decision. For these cases, the 'General notification eCRF' captures the reason for the visit as well as the types of examinations and therapies performed. If during in-office visits the investigator is notified about adverse events, the information is entered into an AE eCRF. To avoid a bias in favor of the control group, which might be introduced as a result of a more complete AE reporting in the BioMonitor group due to possible more frequent contacts, AEs recorded by the investigator during such visits will not be visible to the CRO that performs the regular subject interviews (see section 12.5). Thus it will be possible to estimate a possible underreporting of primary endpoints by looking separately at the information received during the telephone contacts.

8.6 Telephone contact

A telephone contact regimen will be implemented and replace in-office follow-up visits. To obtain endpoint related information, all subjects will receive telephone calls once 4 weeks after enrollment and then every 6 months where they will be asked to answer a study specific questionnaire. In addition, the subject's quality of life will be assessed using the WHO-5 Well-being Index.

The Index was chosen for its:

- Focus on the emotional well-being of the subject
- Applicability during a telephone contact

In addition the EQ-5D-5L questionnaire will be administered during the telephone contacts to gather outcome data for an economic evaluation.

About the EQ-5D-5L:

- The EQ-5D-5L instrument consists of two distinct elements: the EQ-5D descriptive classification system and the EQ visual analogue scale (EQ VAS).
- The descriptive classification system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems.
- The patient is asked to indicate his/her general health state by indicating the most appropriate statement for each of the five dimensions, with each decision resulting in a 1-digit number that expresses the level selected for that dimension. The digits for the five dimensions can then be combined into a 5-digit number that describes the patient's health state. Valuation sets are available for various countries which can then be used to estimate quality-adjusted life-years (QALYs).
- The EQ VAS records the patient's self-rated health on a vertical visual analogue scale, where the endpoints are labelled 'The best health you can imagine' and 'The worst health you can imagine'. The VAS can be used as a quantitative measure of health outcome that reflects the patient's own judgement on the day of measurement.

Telephone follow-up activities and consequent source data tracking will be performed by an external CRO contracted by the main sponsor (see section 12.5). Detailed telephone follow-up guidelines will be provided in a separate document, the 'telephone follow-up manual'. The telephone calls made every 6 months are to be made no earlier than 7 before and 6 weeks after the due date of the telephone contact.

There will also be an initial telephone follow-up within 4 weeks of enrollment. The purpose of this call is for the CRO to introduce themselves to the subject and ascertain the best

time/day to follow up with the subject via phone. AEs will not be assessed during this call; however if the subject spontaneously reports an AE, the CRO will follow up per their guidelines.

If an AE is reported during the telephone contact, then the CRO must forward this information to the respective study site for appropriate follow up and data entry in the EDC system of the reported adverse event(s). The site should try to obtain as much information regarding the adverse event as possible, including all applicable medical records of the event. If the event is an SAE the description of every SAE must be sufficiently documented and confirmed by source data to allow the adjudication by the EAEC. Any event reviewed by the EAEC must have sufficient source documentation to allow for appropriate adjudication.

8.7 Device replacement or explantation

8.7.1 Device replacement

Devices will be explanted according to physician judgment, at the end of battery life or for medical reasons. If the BioMonitor must be replaced due to battery depletion during the study, a replacement of the device is recommended because it is assumed that subject's risk for arrhythmias and endpoints is not decreasing compared to the time of enrollment. The final decision on this topic is left with the discretion of the investigator. The subject shall remain in the study, independent of the decision to replace the device or not.

The ERI form will only be completed when the battery of the device has reached end of life. In case of explantation due to medical reasons, e.g. subject death or implantation of a pacemaker, the reason for explantation will be documented on the respective Adverse Event form.

8.8 Study Termination

The end of study participation of the individual subject will be documented in the Study Termination Form, independent of the reason for termination (see also section 9.2). Reasons for exclusion from the study should be documented as far as possible. All applicable eCRFs shall be completed as far as possible.

After the termination the subject's ongoing medical treatment is to the physician's discretion or should follow the clinical routine.

An official point of explantation of the BioMonitor is not mandated by this study protocol and is therefore solely left with the discretion of the investigator. Hence, in agreement with the subject, the investigator is free to monitor the subject even after her or his official termination from the study.

9. Study Exits

9.1 Drop Out Criteria

A drop-out is defined as any premature termination of a subject's participation in the study before the study termination is formally announced.

Once a subject is enrolled and successfully implanted (if randomized to the BioMonitor group), every effort should be made to continue to follow the subject in the clinical investigation. However, it is inevitable that some subjects will decline to participate further, change geographic location or become non-compliant with the studies requirements.

Drop-out from the study will be considered for the following reasons:

- Subject death (see section 9.1.1)
- Withdrawal of subject informed consent (see section 9.1.2)
- Loss to follow-up (see section 9.1.3)
- Early discovery of a violation of inclusion or exclusion criteria (see section 9.1.4)
- Investigator initiated drop-out (see section 9.1.5)

Applying the intention-to-treat (ITT) principle, subjects considered to be drop-outs are not excluded from the analysis set, except if the conditions described in section 6.1.2 are fulfilled.

Investigator documents the study termination for each subject. Information whether the study termination was regular or premature will be obtained with the study termination eCRF. Moreover, the reason for a premature termination will be documented. Additionally, all status information about ongoing AEs should be documented.

9.1.1 Subject death

In the event of subject death during study participation, personnel at the study site are requested to notify BIOTRONIK, Inc. immediately by completing an adverse event eCRF and a study termination eCRF.

The following information will be required for any subject death in addition to the AE eCRF:

- Death certificate or death report, signed by the investigator, that includes:
    - Date of death
    - Primary cause of death
    - Any other circumstances surrounding the death
    - Whether death was device or procedure related if applicable

Whenever possible, devices should be interrogated prior to the explantation procedure, if possible. If not possible, it is important that the BioMonitor is explanted and returned to the manufacturer for interrogation and analysis. During explantation and shipping, the device should be carefully handled in order to avoid recording false events and allow proper death classification (arrhythmic versus non-arrhythmic death).

All cases of subject death will be adjudicated by the EAEC.

In the event of a cardiac transplantation (HTX), the subject's participation in the study will be terminated. If the subjects did not yet have a primary endpoint, the admission for the HTX procedure will be evaluated as the death of the subject and thus fulfils the criteria for a primary endpoint. HTX will also be contribute to the endpoints of all-cause moratlity and cardiovascular mortality. Secondary endpoints such as the time to first arrhythmia can be assumed to differ significantly between post-HTX and post-MI subjects and should thus not be pooled for analysis.

9.1.2 Withdrawal of subject informed consent

A subject who has consented to participate in the study may withdraw his/her consent at any time without specifying the reason(s) for withdrawal and without disadvantageous consequences for further treatment. Data collected from this subject until the time of withdrawal will be included in the data analysis. The study termination eCRF has to be completed by the study site.

A patient who has consented to participate in the study may withdraw his/her consent for study participation at any time without stating the reason(s) and without any unfavorable consequences. All data collected from this patient until the date of withdrawal will be used in pseudonymized form as long as their further processing or retention is necessary, e.g. to fulfil a legal obligation. This also applies if the patient has requested data erasure. Depending on the patient's will the collected data will be anonymized once further processing or retention is no longer required. A withdrawal sheet and a study termination CRF have to be completed by the investigator.

9.1.3 Lost to follow-up

Subjects lost to follow up are those for whom contact is lost despite best efforts to locate the subjects. In the event a subject is lost to follow up after the CRO has contacted the subject per the guidelines in the telephone manual, the CRO should then contact the study site. Study sites should attempt to contact the subject also and all contact attempts are documented. Study sites are requested to continue attempts to contact until a definitive reason for failure to participate is determined (e.g. subject moved with no forwarding address). In the event the study site is first to determine a subject is lost to follow up, then they should contact the CRO responsible for collecting AEs in an attempt to locate the subject.

In the event the subject cannot be contacted using the above methods, the subject is terminated from the clinical investigation by completing a Study Termination eCRF.

9.1.4 Early discovery of a violation of inclusion or exclusion criteria

If a subject of the BioMonitor group or Control group will be identified to violate any inclusion or exclusion criteria before discharge from the index hospitalization, this shall be considered as premature study termination, which has to be documented on the Termination Form.

9.1.5 Investigator initiated drop-out

The investigator may initiate a premature study termination for legal reasons or if the study participation endangers the subject's well-being or safety. However, a member of the Steering Committee or CI must be consulted before implementation, except in cases of emergency.

In contrast, changes of the subject's treatment, even if related to monitoring or treatment of arrhythmias, do not justify a drop-out, since the subject's further clinical course can be recorded. Two examples are the impossibility to use HM in a new environment of the subject (e.g. moving to a place without mobile phone coverage or admission to permanent care facility or hospice) or the implantation of a pacemaker or implantable cardioverter-defibrillator. These events are no reason to exclude the subject, because the exclusion of such subjects might introduce a bias in favour of the ICM arm.

9.2 Point of enrollment and study termination

The point of enrollment is the time at which a subject signs and dates the informed consent form. Study related procedures, documentation and collection/following of adverse events will start from this day on.

Regular point of termination for all subjects is the date when the formal study termination is announced.

For all non-regular study terminations, the following rules apply:

- In case of subject death, the date of study termination is the date of death.
- In case of HTX, the discharge date from the HTX procedure's hospitalization is the date of study termination.
- In case of withdrawal of consent, the date of study termination is the date of withdrawal of consent.
- If the subject is lost to follow-up, the date of termination is the date of last contact of the investigator or of the CRO that collects AEs. Data from the HMSC will not be

used to ascertain the vital status of subjects for any primary analysis because this might introduce a bias in favor of the BM arm.

- If the subject is defined as drop-out subject for any other reason, the date of study termination is the date on which the reason for the drop-out became effective, i.e. the date on which a violation of inclusion criteria was discovered, or on which the investigator excluded the subject for safety reasons.

Study related procedures and documentation should end at the day of study termination for the respective subject.

10. Additional Study Conditions

10.1 IRB Approval

Institutional Review Board (IRB) approval is required for each study site and investigator prior to participation in this clinical study according to local requirements. Subject enrollment may not begin until both the IRB and BIOTRONIK, Inc. have granted approval for the study site. If IRB approval is withdrawn at any time during the study, BIOTRONIK, Inc. must be notified by the investigator within 5 working days.

10.2 Consent Materials

Prior to the subject's enrollment or participation in the investigation, informed consent is required from all subjects. Informed consent should be obtained in accordance with the FDA regulations (21CFR, Part 50). The informed consent form will comply with FDA regulations (21CFR, Part 50). In addition the subject will be informed on necessary data protection regulation according to European data protection regulation for subject data transferred to the main sponsor located in Europe. The investigator is required to inform BIOTRONIK, Inc. and the reviewing IRB within 5 days if any subject was not appropriately consented to participate in the study. BIOTRONIK, Inc. is then required to report any failure to obtain informed consent to the FDA within 5 working days of learning of such an event. In order to assist with the consent process, BIOTRONIK, Inc. will provide a template consent form to study sites participating in the study. Vulnerable persons (by the investigator’s judgment) will be excluded from participation.

10.3 Other Institutions and Physicians

This clinical study is not transferable to other institutions attended by the investigator unless prior approval is obtained from both BIOTRONIK, Inc. and the appropriate IRB. Only approved investigators are authorized to participate in the clinical investigation. However, there are certain situations where an investigator might not be immediately available to provide the necessary medical care for a subject enrolled in the clinical investigation (such as a subject emergency room visit for medical treatment).

In case technical support is needed the service hotline of BIOTRONIK, Inc. is available 24 hours a day. Phone: 1-800-547-0394.

10.4 Electronic Case Report Forms (eCRFs)

Original data will be collected from each study site and recorded into the EDC system via completion of eCRFs. The investigator will be required to use an electronic signature to approve the content of the data reported in the eCRFs. BIOTRONIK, Inc. will audit and monitor the content of the eCRFs for the US sites as described in section 13.

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

10.5 Handling of Electronic Data

10.5.1 Data protection

The subject must declare in the ICF that he or she agrees to the recording of his or her medical data and their transfer to the main sponsor, the supporting CRO IHF and, if necessary, to responsible IRB. The subject agrees that authorized personnel of the local and main sponsor and the involved IRB (if applicable) may gain insight in the subject record to ensure that the patient was adequately informed about the clinical trial and that the protocol was properly followed.

All subject-related data and information received from the clinical study will be handled confidentially. The collected data will be pseudonymized, without using subject initials, date of birth or other privacy data, to ensure traceability of data, but preventing unauthorized identification of individual subjects. The data will be transmitted to the main sponsor and if necessary to the supporting CRO IHF for electronic data handling, safety reporting and analysis in compliance with applicable regulations.

In addition, all subject data transferred to the main sponsor of this clinical study, CRO, IHF or the respective boards located in the EU (e.g. iMedNet entries, adverse event source data) will be protected in the EU according to the European data protection law (General Data Protection Regulation "GDPR"). The Subject Contact Form containing subject ID code, contact data, name and date of birth will be sent to the telephone follow-up provider (IHF) and archived there.

Copies of the Subject Enrollment Log and Subject Contact Form will not be provided to the sponsor and will remain at study sites. The subjects will be informed their identity and contact information will be available to the investigator and the telephone follow-up provider (IHF).

10.5.2 Data collection

All study-relevant subject data will be documented pseudonymously in eCRF. The established Electronic Data Capture system (EDC) is "iMedNet" of the vendor MedNet Solutions, Inc. as a pure internet-based application that is used with the current versions of most internet browsers, there is no specific local software to support (cloud based "Software as a Service" SaaS). iMedNet supports industry standards (FDA 21 CFR Part 11, HIPAA and EU Commission Decision C (2010)593 Standard Contractual Clauses (processors) and EU-US Privacy Shield Framework).

Use of the EDC system will allow 24 hours 7 days a week access to the module. Site staff with user access will be directed to a page where they will enter their assigned user ID and password in order to access the system. Once these have been validated, there will be options for entering a new subject or new subject data into the system.

For the majority of the eCRF entries source data needs to be maintained at the site and will be collected in adequate files (e.g. subject binder). The data have to be stored and shall be made available upon request in order to allow source data verification.

10.5.3 Procedures used for data review, EDC cleaning, and issuing and resolving data queries

After data entry into the EDC system, the clinical data is automatically checked with programmed quality checks. Additionally, the eCRF will be checked against source data by clinical monitors during periodic monitoring visits as described in the monitoring plan. Errors, discrepancies, missing data, and entries out of range are resolved automatically (in EDC) and manually (clinical monitor, clinical data manager) generated data queries.

The investigational site is obliged to answer all incoming data queries in due time to clarify the open issues. Corrections to the eCRF can only be done by the designated site personnel and have to be signed by an authorized investigator approving thereby the completeness and correctness of the data. The EDC system supports detailed tracking of the query process since all changes are automatically recorded in the system's audit-trail.

Clarification of all open queries is a precondition for site closure in case of premature or regular study termination.

10.5.4 Procedures for verification, validation and securing of electronic data systems

The EDC system is hosted on a dedicated database server at the vendor MedNet Solutions, Inc. Only authorized users with fixed roles have access to the EDC system. The access is controlled and maintained by the Center for Clinical Research (CCR) Clinical Data Management Department of BIOTRONIK SE & Co. KG in coordination with BIOTRONIK, Inc. for US sites. Every access is automatically logged and changes of the clinical data are stored in independent audit trails. The EDC system is verified and validated accordingly. The user interface and the internal business logic is validated accordingly and verified during the study related development and before release for data entry.

An authenticated user account is created and maintained by CC CCR Clinical Data Management of BIOTRONIK SE & Co. KG in coordination with BIOTRONIK, Inc. for each authorized user once the user has completed appropriate training. Users are obligated to keep their password confidential.

Depending on their role within the investigational study, users are limited to "read only" or may be given permits to enter or update data, provide resolutions to queries and apply electronic signatures. Only investigators are allowed to sign the entries.

10.5.5 Data retention and archiving

At end of the study, all study related electronic documents are stored in the archive of BIOTRONIK SE & Co. KG which provides storage conditions free from risk of fire, flood, theft and vermin. The access to the files is controlled. BIOTRONIK, Inc. will be provided access to the archived data.

After EDC database closure, all eCRF data, the audit trail and other relevant EDC content are exported and stored electronically for at least 15 years on an access protected archive server. At the end of this period, requirements from laws and other regulations will be reconsidered in order to decide whether the retention period must be extended or data can be deleted.

10.6 Confidentiality of Subject Data

Information sent to BIOTRONIK, Inc. pertaining to study subjects will be kept confidential at BIOTRONIK, Inc. and is subject to audit by IRB and other regulatory authorities. For reporting purposes, data collected from U.S. sites will be shared with BIOTRONIK SE & Co. KG. Information shared with BIOTRONIK SE & Co. KG will be kept confidential and will be handled by BIOTRONIK SE & Co.KG according to the European data protection regulation (GDPR). Reports submitted to physicians and data presented in publications of study results will not make any reference to subject name.

In order to verify the study data and ensure study integrity, authorized monitors from BIOTRONIK, Inc., authorized personnel from BIOTRONIK SE & Co. KG, regulatory authorities, and the reviewing IRB may review and/or copy the study records. BIOTRONIK will be informed about access to the clinical data for review and copying for external stakeholders.

10.7 Data Quality Control

BIOTRONIK, Inc. will regularly review study data from U.S. subjects. At any time, reports can be generated on entered or missing data by BIOTRONIK, Inc. or by approved research personnel at each study site. The EDC system will be used to track received and expected visit data and eCRFs for each subject. This system also provides the capability to monitor the status, volume, and disposition of data. In addition, all study data will undergo extensive automatic edit and plausibility checks that provide information to the study sites to help improve and maintain data quality control procedures designed to detect inaccuracies and inconsistencies.

10.8 Study Completion

BIOTRONIK, Inc. will notify the study site upon completion or termination of the investigation 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, Inc. will provide a final report to each study site as required by FDA regulations. Monitors may conduct a study closure visit. During this visit, BIOTRONIK, Inc. will verify study records and ensure that the investigator understands any applicable regulatory requirements including those related to record retention. Record storage requirements will be consistent with local regulatory regulations.

11. Benefit/Risk Analysis

11.1 Potential Benefits

11.1.1 Benefits for subjects randomized to the BioMonitor group

As a result of ICM implantation, the heart rhythm of study subjects is closely monitored. Participation in the study may lead to the diagnosis of heart rhythm problems and to a consecutive benefit from prompt treatment of the detected arrhythmias, or the underlying condition of the subject that has caused the arrhythmia.

11.1.2 Benefits for subjects randomized to the control (non-BioMonitor) group

No obvious benefits are expected for subjects randomized to the control group.

11.1.3 Benefits for future subjects

If the study will be successful, it may show that subjects matching the inclusion criteria benefit from ICM monitoring by reducing the risk for MACE. It may thereby contribute to a better treatment of post-infarct subjects. If the study will fail to confirm the primary hypothesis, it may still provide information on subgroups with a benefit that will allow for the planning of confirmatory studies.

11.2 Potential Risks

11.2.1 Anticipated adverse device effects

ICMs are implanted in a subcutaneous position and thus require an invasive implantation procedure. Please see Table 3 for a cumulative listing of the associated risks. On explantation or replacement, which may be required when the battery is depleted or for other reasons, the same risks may apply as for the initial implantation. No data have been identified if the incidence of the listed complications is different for explantation or replacement, when compared to the initial implantation.

Table 3: Surgical Risks

Frequency	**Percentage (%)**	**Risk**
Frequent 1 to 10 patients out of 100	Up to 3[34-37]	local infection at insertion site
	Up to 3[35]	superficial infection at insertion site
	Up to 1,9[37]	irritation or inflammation at insertions site
	Up to 1,2[34]	local erosion at insertion site
	Up to 1,5[35]	erythema at insertion site
	Up to 1,5[34-37]	persistent pain at inframammary implant site
	Up to 3[36]	difficulties at device interrogation
	Up to 5[36]	device migration
	Up to 2,3[34;36]	device repositioning
	Up to 2,4[34-37]	device explantation (unplanned)
Not known Frequency not assessable on the basis of the available data	heating, swelling of the skin, impairment of wound healing, bleeding, hematoma	

However, it is important to state that ICMs do not require vascular access or direct contact with the endocardium. Consequently, ICMs do not carry the same risk of endocardial complications known from pacemakers or ICDs [38;39].

The safety of ICMs has been investigated in many studies with regards to syncope and AF management [40]. It has been demonstrated successfully that the strategy of prolonged monitoring in patients with Cardiac Implantable Electronic Devices (CIED) is safe [41].

Moreover, the safety of the BioMonitor and BioMonitor 2 was the objective of several completed studies. These studies found a very low device-related event rate ranging from 0% to 2.2%. The procedure-related event rate, including events such as pocket infections, pain around the pocket, and swelling of pocket due to hemorrhage, were compatible with the event rates presented in Table 3.

Automatic ICM recording and wireless transmissions are feasible for remote ECG monitoring but can be accompanied by a remarkable rate of false detections. This may lead to memory saturation and loss of information about true episodes. However, with the remote monitoring feature it is possible to identify these subjects and take corrective actions during an in-office visit, i.e. re-programming of the device settings.

11.2.2 Risk associated with participation in the study

Apart from the anticipated adverse device effects discussed in section 11.2.1, no additional risks are associated with participating in this study. Investigators will decide upon therapies based not on ICM diagnosis, but upon thorough examination of the subject after the ICM has detected relevant arrhythmias. These therapies will be based on evidence-based guideline recommendation. Thus, it is not to be expected that the study will lead to unneeded or harmful therapeutic intervention.

11.3 Steps to control or mitigate the risks

Risks associated with the BioMonitor (see section 11.2.1) have been reduced by special risk reduction measures listed in the technical manual.

Among others, the risk is minimized through the utilization of strict aseptic technique, close monitoring of the subject's physiologic status during the implantation procedure and compliance with the technical manual. Moreover, with regards to risk control it will be crucial to follow this protocol in all aspects and to promptly supply the sponsors with all pertinent information required by this protocol.

11.4 Risk-to-benefit rationale

The investigational device is approved in Europe for standard medical care (CE mark) and within the United States (FDA clearance). It is not anticipated that the subjects participating in this study are exposed to any risks beyond those stated in section 11.2.1. Moreover, most risks associated with the implantation of the BioMonitor can be solved with non-invasive measures, and even if not, can typically be resolved without sequelae.

The BIO|GUARD-MI study is expected to provide additional insights regarding the reduction of the risk for MACE. These insights may be applied to future patients after MI. Therefore, the anticipated risks seem to be justified when compared to the potential benefit of the study.

12. Study Oversight

The sponsor will offer, if needed, technical support and training to the investigator e.g. for the implantation, interrogation or programming of the BioMonitor.

External boards, committees and vendors contracted by the sponsor will be responsible for:

- Assessment of the primary endpoint (see section 12.1)
- Safety monitoring (see section 12.2)
- Overall guidance of the clinical investigation (see section 12.3)
- Coordination of the publication process (see section 12.3)
- Home Monitoring analysis (see section 12.4)
- Telephone follow-up activities (see section 12.5)
- Coordination of the publication process (see section 17)

12.1 Responsibilities of the Endpoint and Adverse Event Board (EAEC)

The EAEC will define the criteria for primary endpoint evaluation and will analyze all cardiovascular adverse events and all cases of subject death with respect to the specified endpoint criteria. Additionally, the EAEC will periodically review a listing of all AEs which occurred during the course of the study with regards to their potential contribution to the primary endpoint. Details with regards to the specific process will be determined in the EAEC charter.

12.2 Responsibilities of the Data Safety Monitoring Board (DSMB)

The DSMB will review accumulating study data to address subject safety and ethical issues of the study. If applicable, the DSMB will initialize and supervise the two interim analyses and the final analysis of the primary endpoint. Based on the interim data, the DSMB will give the request to stop the clinical investigation for superiority or give a recommendation to the steering committee and the sponsor whether to continue the clinical investigation as planned, to adapt the sample size, or to stop the clinical investigation for futility. Details with regards to the specific process will be determined in the DSMB charter.

12.3 Responsibilities of the Steering Committee

The steering committee will provide overall guidance of the clinical investigation. Therefore it is responsible for the scientific validity of the protocol and the assessment of quality in

course of the study. The steering committee will identify and approve members of the DSMB and EAEC and will monitor their activities during study conduct. Details with regards to the specified tasks and responsibilities will be determined in the steering committee charter.

12.4 Responsibilities of the Central Electrocardiogram Monitoring Board (CEMB)

Home Monitoring analysis will be performed by a CEMB.

All incoming Home Monitoring data are evaluated centrally by the CEMB in accordance with the criteria defined in the CEMB charter. Accordingly, the CEMB will inform the respective study site in a timely manner about relevant arrhythmia detections (see section 8.5). Details with regards to the specific process will be determined in the CEMB charter.

12.5 Responsibilities of the Contract Research Organization (CRO)

An external service provider has been appointed to perform the telephone follow up interviews of all subjects 4 weeks following enrollment and then every six months until study termination (see section 8.6). Furthermore they will inform the respective site about potential AEs and will organize and support the collection of relevant source data. Details with regards to the specified tasks and responsibilities will be determined in the 'telephone follow-up manual'.

The appointed service provider is:

IHF GmbH

Institut für Herzinfarktforschung

Bremserstraße 79

67063 Ludwigshafen

Germany

In the course of the study additional service providers might be contracted to serve included countries.

12.6 Responsibilities of the coordinating investigator (CI)

Responsibilities of the coordinating investigator are among others:

- Give input and advice for the protocol creation and possible amendments, medical review

- Consulting and support in case of clinical or organizational issues arising during the conduction of the study
- Advising all investigators in medical questions connected to the study

13. Study Monitoring

13.1 Methods

The responsibility of BIOTRONIK, Inc. as local sponsor is to ensure protocol and regulatory compliance through proper monitoring of the clinical investigation in U.S. sites. BIOTRONIK, Inc. is also required to ensure that the investigational device is used under the immediate direction of an investigator. As the investigator, the physician is responsible for conducting the clinical investigation 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 primary investigator must also accept responsibility for all aspects of the clinical investigation including the actions of any co-investigators participating in the clinical investigation at the investigational site.

The entries in the eCRF will be reviewed and source data verified at the investigational site or remotely by monitors (authorized BIOTRONIK, Inc. personnel, Clinical Research Associates-CRAs, or by authorized BIOTRONIK, Inc. designees) to ensure that the investigator and the clinical investigation team conducts the clinical investigation in accordance with the clinical investigation 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, Inc. may require the presence of personnel from BIOTRONIK, Inc. at implant and/or follow-up visits outlined in this protocol in order to assist the investigator and other site personnel.

A detailed monitoring plan developed by BIOTRONIK will be followed. Monitors will visit the study site periodically during the clinical investigation in accordance with the monitoring plan.

13.2 Monitors

Monitors are trained, qualified, and designated by BIOTRONIK, Inc. management to oversee the progress of a study at the clinical site.

Periodic monitoring visits will assure, amongst others, that the facilities are still acceptable; that the protocol is being followed, that the IRB has been informed about approved protocol changes as required, that records on study conduct and data collection are complete and present, that appropriate and timely reports have been made to the sponsor, IRB, and other authorities, and that the investigator is carrying out all agreed activities.

Periodic monitoring visits, assessments of the study site will include but will not be limited to the following:

- Completion and submission of the required electronic case report forms (eCRFs) and other applicable study documentation
- Continued acceptability of the facilities

- Adherence to the clinical investigation plan
- Adherence to applicable FDA and/or local regulations and laws

If a monitor becomes aware that an investigator is not complying with the requirements mentioned above, the monitor is obliged to notify BIOTRONIK, Inc. study management. BIOTRONIK, Inc. will evaluate the non-compliance and issue corrective actions, discontinue enrollment or as a last measure close the clinical investigation site.

14. Deviations from Clinical Investigation Plan

All sponsor personnel, all investigational site personnel as well as other third parties, who are involved in tasks covered by this protocol, are generally obliged to comply with this protocol. The investigator is required to conduct this study in accordance with the signed investigator agreement and clinical protocol. The investigator shall notify BIOTRONIK, Inc. and reviewing IRB in writing no later than 5 working days after any significant deviation from the clinical protocol that has occurred to protect the life or physical well-being of a subject in an emergency. Except in such emergency situations, prior approval by BIOTRONIK, Inc. is required for significant deviations from the clinical protocol.

14.1 Recording deviations

Study sites will be requested to inform the sponsor about any deviation as they become aware of the deviation. In addition, compliance to the protocol will be verified by the sponsor at monitoring visits. Each site specific deviation is recorded within the EDC system on a Protocol Non-Compliance (PNC) eCRF. The sponsor will assess for the need of corrective or preventive actions. Additional information on the type of deviation, actions taken and outcome should be recorded in the monitoring visit reports. The deviations should be discussed with the PI or authorized designee and re-training may be performed to prevent further deviations. Retraining will be documented accordingly when completed. Other additional suitable actions may be initiated after consultation of the clinical project management.

Deviations by sponsor personnel or third parties are reported immediately to the sponsor by anyone who becomes aware of it. They will be assessed for the need of corrective or preventive actions.

14.2 Reporting Deviations

All deviations will be reported in the interim and final clinical investigation reports.

Study sites will be requested to inform the sponsor about any deviation as they become aware of the deviation. In addition to reporting deviations to BIOTRONIK, Inc., certain types of deviations may also require IRB notification.

BIOTRONIK, Inc. categorizes protocol non-compliance instances as either protocol violations or protocol deviations. Both protocol violations and deviations will be reported in the interim and final clinical progress reports.

14.2.1 Protocol Violations/Major Deviations

Protocol violations are major deviations 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 study and/or the rights, safety, or welfare of subjects. Protocol violations include, but are not limited to, failure to obtain consent, unapproved investigator implanting a device, and subject inclusion/exclusion violations.

The investigator must notify the reviewing IRB of all protocol violations per the reporting requirements. In some instances, such as failure to obtain consent, the investigator should also seek guidance from the IRB to ensure the subject received appropriate information to consider their participation in the study.

14.2.2 Protocol Deviations

Protocol deviations not meeting the definition of a violation are generally less serious in nature and may not require IRB notification as long as they do not affect the rights, safety, or welfare of the study subject.

14.3 Corrective and preventive actions and disqualification criteria

Corrective actions are taken in order to repair or to avoid any negative consequences caused by a deviation. Preventive actions are taken to avoid that the same sort of deviation reappears.

Every individual deviation is assessed by the sponsor for the need of appropriate action. In addition, the sponsor regularly evaluates the reported deviations to identify the need of general preventive actions.

All persons involved in a deviation have to co-operate with the sponsor in identifying and implementing the appropriate actions, if necessary. Disqualification of study personnel or investigational sites is the ultimate escalation step of preventive actions. This means that in case of major deviations that seriously affect the safety and well-being of subjects or that bear a high risk of refusal of the clinical data and mistrust to the results of the study and that are likely to reappear despite other actions, the responsible person or investigational site is excluded from further conduct of the study, unless this exclusion would jeopardize the rights, safety or welfare of the subjects.

15. Adverse Events

In the course of the clinical investigation, undesired medical events can occur in participating subjects, which are called adverse events (AEs). Furthermore, device deficiencies (DD) or complaints may also be observed. All AEs and device deficiencies and complaints of the investigational device shall be assessed by the investigator and shall be documented and reported throughout the clinical investigation.

Adverse event reporting starts with the signing of the Informed Consent Form. The responsible investigator has to evaluate and report any AE that is brought to his/her attention during the course of the study. All AEs must be documented on the corresponding eCRF. Investigators have to adhere to notification timelines as outlined below and in section 16.2.

15.1 Definitions

15.1.1 Definition of Adverse Event

An AE is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons whether or not related to the investigational medical device. This includes:

- Events related to the medical device or the comparator
- Events related to the procedures involved
- For users or other persons, this definition is restricted to events related to the medical devices.

The following conditions will not be considered as an Adverse Event in terms of this study:

- Preexisting conditions unless the health status of the subjects worsens during the course of the study
- Explantation of the BioMonitor due to battery depletion when in accordance with expected longevity

Arrhythmias that occur for the first time in a subject during the course of the study will be reported once at initial detection. For repeated episodes of the same arrhythmia no further AE reports will be necessary unless the condition deteriorates into a serious adverse event.

15.1.2 Definition of Adverse Device Effect

An adverse device effect (ADE) is an AE that is related to the use of an investigational medical device. This includes any AE resulting from insufficient or inadequate instructions for use or the deployment, implantation, installation, or operation, or any malfunctioning of

the investigational device and any event resulting from use error or from unintentional misuse of the investigational device.

Adverse events, which result from the required medical procedures involved, when implanting, using or testing the respective investigational device, even if not directly related to the device (e.g. anesthetic complications, wound healing disturbances, etc.) are considered ADEs.

15.1.3 Definition of Unanticipated Adverse Device Effects

As defined in 21 CFR Part 812.3, an unanticipated adverse device effect (UADE) is any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem or death was not previously identified in nature, severity or degree of incidence in the study protocol or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of subjects. A root-cause analysis will be performed and the possibility of reoccurrence will be evaluated immediately.

A listing of previously identified adverse events along with anticipated frequency is provided in section 11.2.1. It is important to note that random component failures or problems caused by misuse of the product are not considered unanticipated adverse device effects.

15.1.4 Definition of Serious Adverse Events

AEs are classified as serious if one or more of the following consequences are fulfilled:

- led to death
- led to serious deterioration in the health of the subject, that either resulted in
  - a life-threatening illness or injury, or
  - a permanent impairment of a body structure or a body function, or
  - in-patient or prolonged hospitalization, or
  - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
- led to fetal distress, fetal death or a congenital abnormality or birth defect.

Note: Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered a serious adverse event.

In-patient hospitalization is defined as at least one overnight stay (change of date) in a hospital. Events for which subjects are hospitalized for less than 24 hours without change of date will not be documented as serious, unless one or more of the other seriousness criteria are fulfilled.

According to national and international requirements some of the involved Competent Authorities (CA) and Ethics Committees (EC) have to be informed on the occurrence of SAEs during the course of the study. In general, this duty will be fulfilled by the main sponsor if not requested otherwise by the EC or CA. The investigator is obliged to provide all relevant information on the SAE in a timely manner and to follow all SAEs until the date of their resolution.

For OUS reporting requirements, SADEs are defined as unanticipated if by their nature, incidence, severity or outcome they have not been identified in the current risk analysis. These events must be reported to the main sponsor immediately. A root-cause analysis will be performed and the possibility of reoccurrence will be evaluated immediately.

15.1.5 Definition of Serious Adverse Device Effect

An ADE that resulted in any of the consequences characteristic of a serious adverse event is considered serious.

15.1.6 Definition of Unanticipated Serious Adverse Device Effects

SADEs are defined as unanticipated if by their nature, incidence, severity or outcome they have not been identified in the current risk analysis.

These events must be reported to the sponsor immediately.

A root-cause analysis will be performed and the possibility of reoccurrence will be evaluated immediately.

Note: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the current risk analysis.

15.1.7 Definition of Device Deficiency

Device deficiency (DD) is defined as inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance, including malfunctions, use errors and inadequate labelling.

DDs of the investigational device shall be documented throughout the study. DDs which caused an AE are reported on the respective Adverse Event eCRF. In the case the DD did not cause an adverse event, the Device Deficiency eCRF shall be used to document this "non-medical" event.

If a "non-medical" DD could have led to a SADE,

- if either suitable action had not been taken,
- if intervention had not been made, or
- if circumstances had been less fortunate,

the DD or complaint is classified as having SADE potential.

15.1.8 Definition of Device Complaint

A device complaint is any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a device after it is released for distribution. If the Device Complaint is caused by an AE, then the Device Complaint that caused the AE will be reported on the respective Adverse Event eCRF. In the event the Device Complaint did not cause an adverse event, the Device Deficiency eCRF shall be used to document this "non-medical" event.

15.2 Causality Assessment

The relationship between the use of the investigational device (including the surgical procedure) and the occurrence of each adverse event shall be assessed and categorized, considering the presence of confounding factors, such as concomitant medication/treatment, the natural history of the underlying disease, other concurrent illness, or risk factors. Each AE will be classified according to five different levels of causality. The investigator will use the following definitions to assess the relationship of the adverse event to the investigational medical device or procedures and the sponsor will review the investigator's categorization:

- **Not related:** the relationship to the device or procedures can be excluded.
- **Unlikely:** the relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
- **Possible:** the relationship with the use of the device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.
- **Probable:** the relationship with the use of the device seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained.
- **Causal relationship:** the serious event is associated with the device or with procedures beyond reasonable doubt.

The investigators will distinguish between the adverse events related to the investigational device and those related to the device procedures (any procedure specific to the investigational device). Procedure related events refer to the procedure related to the application of the investigational medical device only and therefore not to any other

procedure for other devices and not to any other procedures or treatments applied later throughout the clinical investigation, for instance to treat adverse events.

Note

- In case of a replacement of the device in response to an adverse event (the BioMonitor is replaced), the replacement will be considered like an initial application of a new device and shall be assessed accordingly.
- Replacement of the BioMonitor due to regular battery depletion is not considered an adverse event.
- An adverse event can be related both to procedures and the device. Complications of procedures are considered not related if the said procedures would have been applied to the patients also in the absence of device use or application.

15.3 Reporting responsibilities

15.3.1 Reporting responsibilities of the investigator to sponsor

The investigator shall document all events on the respective eCRF pages provided within the EDC system. The timelines for reporting of initial cases and possible update reports are indicated in Table 4. Due to the reporting requirements in the EU, all adverse events shall be reported with an assessment in accordance with ISO14155. Reporting requirements per FDA requirements will also be observed.

The reports shall be done with all information available, even if this results in an incomplete report. The investigator has to follow-up ongoing (S)A(D)Es either as long as the subject participates in the study, the clinical investigation is terminated or until the event has been resolved, whatever comes first.

Multiple events may occur simultaneously in one subject. For each medically independent event with a primary diagnosis an individual report must be provided. In addition, the action taken/ treatment should also be provided with any supportive documentation available. The investigator has to ensure that all relevant information is available. This also includes information from other parties (family, other hospitals etc.).

If a subject dies during the study, the investigator shall document the cause of death, circumstances and place of death. All actions taken, which were initiated to gain further information must be documented in writing and provided to BIOTRONIK.

Reporting responsibilities of the sponsor

To ensure reporting requirements are met during the study, adverse event information reported for all study sites, both those within the U.S. and outside of the U.S., will be

reviewed by BIOTRONIK, Inc. and BIOTRONIK SE & Co. KG to ensure region specific reporting requirements are met.

As such, unanticipated adverse device effects identified outside of the U.S. will be reported to FDA, all reviewing IRBs, and participating investigators per the standard requirements and timelines.

Conversely, BIOTRONIK SE & Co. KG will report all serious adverse events, serious adverse device effects, unanticipated serious device effects and all device deficiencies with serious adverse device effect potential that are identified at a U.S. site to the competent authorities and investigators as required and depending on the local regulatory requirements.

16. Records and Reports

16.1 Investigator Records

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

- All correspondence relating to the study with another investigator, an IRB, BIOTRONIK, Inc., a monitor, or any regulatory agency (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 research study
- A copy of the IRB approved subject Informed Consent Form
- All clinical forms and documentation, including:
  - A copy of all signed subject Informed Consent Forms
  - All supporting documentation for data entered into the EDC system
  - Records of any adverse events, adverse device effect, or device deficiency/complaint, 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, Inc.

The investigator must retain records related to the study according to FDA regulations, IRB requirements and local regulatory regulations.

16.2 Investigator Reports

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

- Notification of a subject death during the study
- Any unanticipated adverse device effects
- Notification of the withdrawal of IRB approval
- Annual progress reports prepared for the IRB
- Notification of any deviations from the clinical protocol

- Notification that informed consent was not obtained from a subject
- Final summary report prepared for the IRB
- Any other information upon the request of an IRB, FDA, other regulatory authority, or BIOTRONIK, Inc.

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

Table 4: Investigator Reporting Responsibilities

Type of Report	Investigator Reporting Responsibilities	
	Report Prepared For	Reporting Timeframe
FDA-Defined Reports		
Unanticipated adverse device effect	Sponsor IRB/EC*	As soon as possible, upon awareness of the effect. Within 10 working days after the investigator first learns of the effect
Unanticipated serious adverse device effect	Sponsor IRB/EC*	As soon as possible, upon awareness of the effect. Within 24** hours after the investigator first learns of the effect.
Device deficiencies	Sponsor IRB/EC*	Within 14 days after the investigator first learns of the effect.
Device complaints	Sponsor IRB/EC*	Within 14 days after the investigator first learns of the effect.
Withdrawal of IRB/EC approval or other action on part of the IRB/EC that affects the study	Sponsor	Within 5 working days of receipt of notice of withdrawal of approval
Subject death	Sponsor and IRB/EC*	As soon as possible upon awareness of death
Progress reports	IRB/EC*	At regular intervals, but in no event less than yearly.
Significant deviations from investigational plan	Sponsor and IRB/EC*	**Emergency**: ASAP but in no event later than 5 working days after emergency occurs to protect the life or physical well-being of a subject in an emergency. **Non-emergency**: prior approval by Sponsor and, if deviation may affect scientific soundness of the trial or the rights, safety or welfare of subject, also by the IRB/EC and FDA as an IDE supplement.
Informed consent not obtained	Sponsor and IRB/EC*	Within 5 working days of use of the investigational device.
Final report	Sponsor and IRB/EC*	Within 3 months after termination or completion of study or termination of site's participation.

Other Reports		
Adverse Events (AE)/Adverse Device Effect (ADE)	Sponsor and IRB/EC*	Within two weeks of site notification of AE/ADE
Device deficiencies with SADE potential***	Sponsor IRB/EC*	As soon as possible, upon awareness of the deficiency. Within 24** hours after the investigator first learns of the effect
Serious Adverse Event (SAE)/Serious Adverse Device Effect (SADE)***	Sponsor IRB/EC*	Immediately upon site notification. At latest, 24 hours after notification.

ASAP: as soon as possible; EC: Ethics Committee; FDA: Food and Drug Administration; IDE: investigational device exemption; IRB: Institutional Review Board.
* Reporting to IRB/EC only where required by local legal requirements.
** FDA requires 10 working days.
***Term not defined by FDA.

16.3 Sponsor Records

BIOTRONIK, Inc. will maintain the following records:

- All correspondence with the investigator(s), IRBs, and FDA that pertains to the study
- Investigator agreements, financial disclosures, and current curriculum vitae
- Name and address of each investigator and each IRB that is involved with the investigation
- Adverse events and complaints
- Adverse device effects (whether anticipated or unanticipated)
- Electronic Case Report Form data
- Confirmation of completed subject informed consent forms
- Clinical investigation protocol and report of prior investigations
- Screening visit reports
- Monitoring reports
- Clinical progress reports
- Statement of the extent to which the good manufacturing practice regulation in part 21 CFR 820 will be followed in manufacturing the device

16.4 Sponsor Reports

BIOTRONIK, Inc. is responsible for preparing the following reports, when necessary, as listed in Table 5.

Table 5: Sponsor Reporting Responsibilities

Type of Report	Prepared by BIOTRONIK, Inc. for	Time Constraints of Notification
Unanticipated adverse device effect	FDA, all reviewing IRBs, participating investigators	Within 10 working days after notification of effect
Withdrawal of IRB approval	FDA, all reviewing IRBs, participating investigators	Within 5 working days of receipt of notice of withdrawal of approval
Withdrawal of FDA approval	Reviewing IRBs, participating investigators	Within 5 working days
Current investigator list	FDA	Names and addresses of participating investigators at 6 month intervals
Progress report	FDA, all reviewing IRBs	Submitted at least annually
Recall and disposition	FDA, 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	FDA, all reviewing IRBs, participating investigators	Notification within 30 working days of the completion or termination of the investigation. A final report will be submitted within 6 months after completion or termination of the study.
Informed consent not obtained	FDA	Within 5 working days of notification of occurrence

17. Publication policy

17.1 Publication Steering Committee

A Publication Steering Committee (PSC) is constituted when the protocol is finalized. It may include the Coordinating Investigator (CI), members of the Steering Committee, investigators and other individuals who have expertise in the area and employees of BIOTRONIK. All study stakeholders (e.g. participating investigators, Steering Committee members, BIOTRONIK employees) may submit publication ideas through the PSC. Based on a charter, the PSC would develop a publication strategy and oversee the development of publications and abstracts/presentations according to the publication strategy. All manuscripts and abstracts will be reviewed and approved by the PSC, all authors and BIOTRONIK. The PSC makes decisions about the authorship and writer(s). Members of the PSC may become authors but membership does not automatically result in authorship. The PSC will meet approximately every year to refine the publication strategy.

17.2 Authorship guidelines

17.2.1 Purpose

Purpose of this guideline is to settle criteria to determine which of the contributors to an article in a peer reviewed journal or an abstract for a scientific congress based on data from the BIO|GUARD-MI study should be identified as authors.

Criteria of journals or congresses may differ from these guidelines. In this case, requirements of journals or congresses are to be respected.

17.2.2 Validity

This authorship guideline is valid for all contributors to an article or abstract, including investigators taking part in the study, sponsor employees, and individuals contracted by the sponsor. All authors listed on an article or abstract must fulfill authorship criteria listed below and should sign this agreement. On the other hand, all persons fulfilling the authorship criteria listed below shall be considered for authorship.

17.2.3 Authorship criteria

Authorship of all publications will be decided by the Publication Steering Committee (PSC).

Authorship will be determined prior to the development of a publication or presentation. Authorship credit should be based on all of the following conditions with regard to the International Committee of Medical Journal Editors (ICMJE):

- substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data,
- drafting the article or revising it critically for important intellectual content, and
- final approval of the version to be published.

The PSC will assure that the assessment of the contribution of all potential authors will be fair. Especially, the PSC will weigh the importance of a potential author's contribution to the study data, his or her membership on committees and boards, and his or her contribution to the publication idea or the discussion of the publication's content.

17.2.4 Justification and rules for the assessment of "acquisition of data"

Study specific criteria for *acquisition of data* have been defined. A scoring system will consider two components: enrollment of subjects and the complete documentation of the reaction to HM containing the classification of an arrhythmia detected by the ICM, the resulting subject contact and, if a change in therapy is indicated, also the documentation of the therapy changes.

Enrollment: The importance of subject enrollment for the success of the study is obvious. All subjects are counted if they are randomized and included in the analysis population.

Reaction to HM: The thoroughly conducted diagnostic work-up and consequent treatment, if required, after ICM detected arrhythmias is the mechanism by which the study attempts to improve the outcome in the treatment arm. Since the study does not enforce therapy, documented cases of arrhythmia and subject contact will be acknowledged independent of the question whether it resulted in a therapy or not.

Besides the assumed influence on the primary study outcome, the complete documentation of event chains is an important secondary objective of the study.

To be counted, the following requirements must be fulfilled:

- An arrhythmia reported by the CEMB was classified by the investigator
- The subject was contacted, if applicable
- If a diagnostic work-up was considered necessary, the diagnostic results and therapy changes are reported
- The overall delay from CEMB report to classification by the investigator did not exceed 7 days
- The information was recorded in the corresponding eCRFs and no open queries remain at study termination.

To calculate the value of reaction to HM cases, the following rules apply: The time from CEMB notification to subject contact must not exceed 7 days. W*ithin this period, the*

investigator must have studied the HM content and classified the subject's rhythm, and must have contacted the subject, if applicable.

If this timeline is met, the full value is granted for the case.

17.2.5 Calculation of the total score

For all randomized subjects together, 1000 points are granted. For each randomized subject, the number of granted points to the study site is 1000 divided by the number of randomized subjects.

For all Reaction to HM cases fulfilling the defined conditions together, 1000 points are granted. For each case, the value granted to the study site is 1000 divided by the total number of cases. These points may be reduced if the delays occurred, as defined above.

The points are added for all study sites. If, for example 3000 subjects will be enrolled and 5000 cases of arrhythmia and contact are documented, all sites will receive 0.33 points per enrolled subject, and 0.2 points per timely documented event chain.

The sites will then be ranked by the number of points.

17.2.6 Authors' tasks and responsibilities

This will include but may not necessarily be limited to the following:

First author

a) Guarantor for the integrity of the study BIO|GUARD-MI and its report
b) Lead for writing and managing the manuscript/abstract
c) Submit the manuscript/abstract to allocated reviewers (co-author, BIOTRONIK etc.) according to the publication plan
d) Preparation and submission of the manuscript/abstract according to timelines, defined in the publication plan
e) Adaptation of the manuscript, based on Journal reviewer feedback
f) Disclose potential conflicts of interest

Co-authors

a) Assist the first author in planning and writing the publication, if needed
b) Review of the manuscript/abstract and give feedback within the determined time window
c) Agree on the order in which they appear in the manuscript/abstract
d) Agree on any changes in authorship
e) Disclose potential conflicts of interest

17.2.7 Authorship of ancillary publications

Ancillary publications are publications, which are not part of the publication strategy. The PSC must approve ancillary requests and will need to ensure, that these publications do not present conflicts with other planned publications or earlier submitted requests. Requests for ancillary publications will be evaluated for scientific validity and the ability of BIOTRONIK to provide resources. All manuscripts and abstracts will be reviewed and approved by the PSC, all authors and BIOTRONIK. The PSC may decide on a different scoring system which should, in this case, favor investigators who have contributed more data to the specific subject of the publication.

17.2.8 Contributorship and acknowledgement

Individuals, including BIOTRONIK employees, who have substantially contributed to a study, but who do not meet the authorship criteria, should be listed in the acknowledgement section. Any support provided by non-BIOTRONIK-personnel, e.g. a professional medical writer must also be disclosed in the acknowledgement section.

17.2.9 Timelines

The publication plan gives a detailed overview of timelines for preparation and submission of publications. If the first author will not provide a manuscript within appropriate time after following reminder, a co-author will be invited to become first author.

17.2.10 Compliance

The Publication Steering Committee will ensure that authorship guidelines are met and authorship is attributed appropriately. The Publication Committee will also track timeline adherence.

17.2.11 Reimbursement

No honoraria will be paid for authorship of publications.

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19. List of Abbreviations

ADE	Adverse Device Effect
AE	Adverse Event
AF	Atrial Fibrillation
AMI	Acute Myocardial Infarction
ASADE	Anticipated serious adverse device effect
ANF	Arrhythmia Notification Form
AV	Atrioventricular
BMI	Body Mass Index
CA	Competent authority
CI	Coordinating Investigator
CE	CE mark, a stylized "CE" (Conformité Européenne) placed on products to signify conformance with European Union regulations
CEMB	Central Electrocardiogram Monitoring Board
CFR	Code of Federal Regulations
CHADS	congestive heart failure, hypertension, age, diabetes, stroke
CI	Confidence Interval
CIED	Cardiac Implantable Electronic Device (ICD, PM, CRT (D) + ICM)
CRO	Clinical Research Organization
DD	Device Deficiency
DSMB	Data Safety Monitoring Board
e.g.	exempli gratia
EAEC	Endpoint and Adverse Event Committee
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EF	Ejection Fraction
ESC	European Society of Cardiology

FDA	US Food and Drug Administration (www.fda.gov)
GCP	Good Clinical Practice
GDPR	EU General Data Protection Regulation
H_0	Null Hypothesis
H_A	Alternative Hypothesis
HIPAA	Health Insurance Portability and Accountability Act
HM	Home Monitoring
HMSC	Home Monitoring Service Center
HVR	High ventricular rate
HR	Hazard ratio
i.e.	Id est
ICD	Implantable Cardioverter Defibrillator
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (www.ich.org)
ICM	Implantable Cardiac Monitor
ICS	Implant Control System (e.g. BIOTRONIK's ICS 3000)
ID	Identification Number
IHF	Provider of telephone follow-up services (IHF GmbH Institut für Herzinfarktforschung)
IRB	Institutional Review Board
ISO	International Organization for Standardization (www.iso.org)
LVEF	Left Ventricular Ejection Fraction
MACE	Major Adverse Cardiac Event
MedNet	Supplier of Clinical Trial Software (MedNet Solutions, Inc. www.mednetstudy.com)
MI	Myocardial Infarction
NSTEMI	non-ST Segment Elevation Myocardial Infarction
NYHA	New York Heart Association

PCI	Percutaneous Coronary Intervention
PID	Product ID
PI	Principal Investigator
PMCF	Post Market Clinical Follow Up
PPV	Positive Predictive Value
PSC	Publication Steering Committee
QoL	Quality of Life
QRS	Electrical complex on an ECG related to the depolarization of the ventricles
Saas	Software as a Service
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAS	Statistics and Analysis Software produced by SAS Institute Inc. (www.sas.com)
SAP	Statistical Analysis Plan
sECG	subcutaneous Electrocardiogram
STEMI	ST Segment Elevation Myocardial Infarction
TIA	Transient Ischemic Attack
VF	Ventricular Fibrillation
VT	Ventricular Tachycardia
WHO	World Health Organization