BIOTRONIK
excellence for life

Clinical Investigation Plan

BIO|GUARD-MI Study

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

Reference Number HS058

Version 7.0

April 06, 2021

Coordinating Investigator (CI)

[redacted]

Rigshospitalet
Hjertecentret
Blegdamsvej 9
DK - 2100 Copenhagen
Denmark

„Leiter der klinischen Prüfung" (LKP) in Germany

[redacted]

Vivantes Humboldt Klinikum
Am Nordgraben 2
13509 Berlin
Germany

Director, Clinical Project Management

[redacted]

BIOTRONIK SE & Co. KG
Center for Clinical Research
Woermannkehre 1
12359 Berlin
Germany

Senior Clinical Project Manager

[redacted]

BIOTRONIK SE & Co. KG
Center for Clinical Research
Woermannkehre 1
12359 Berlin
Germany

Team Leader Vigilance and Regulatory Support

[redacted]

BIOTRONIK SE & Co. KG
Center for Clinical Research
Woermannkehre 1
12359 Berlin
Germany

[redacted]

[redacted]

Biometrician/Statistician

[redacted]

BIOTRONIK SE & Co. KG
Center for Clinical Research
Woermannkehre 1
12359 Berlin
Germany

Senior Clinical Scientist

[redacted]

BIOTRONIK SE & Co. KG
Center for Clinical Research
Woermannkehre 1
12359 Berlin
Germany

Sponsor

BIOTRONIK SE & Co. KG
Woermannkehre 1
12359 Berlin
Germany

Local SponsorUS

BIOTRONIK Inc.
6024 Jean Road
US-97035 Lake Oswego

A current list of participating investigators, investigational sites, and institutions and a detailed list of sponsor contacts are filed in the Central File.

Signature of the Principal Investigator

Name: _____

Institution: _____

_____

Street: _____

ZIP code/ City: _____

Country: _____

- I carefully read and fully understood the clinical investigation plan (CIP). I agree to conduct the study according to the clinical investigation plan, the Declaration of Helsinki, ISO 14155 and all other applicable legal requirements.
- I understand that changes to the clinical investigation plan may only be performed after consultation of the coordinating clinical investigator, the clinical project management and after amendment submission and approval by the ethics committee and regulatory authorities (if applicable).
- I agree to inform all involved personnel on the requirements of the clinical investigation plan and ensure that the study will be conducted according to the CIP.
- I agree to report every occurring Adverse Event and Device Deficiency according to the timelines and regulations indicated in the CIP.

_____ _____

City, date Signature of Principal Investigator

TABLE OF CONTENTS

1 LIST OF ABBREVIATIONS

ACS	Acute coronary syndrome
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
bpm	Beats per minute
CA	Competent authority
CAG	Coronary angiogram
CI	Coordinating Investigator
CDMS	Clinical Data Management System
CDW	Clinical Data Warehouse
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)
CIP	Clinical Investigation Plan
CIR	Clinical Investigation Report
CRA	Contract Research Associate
CRF	Case Report Form
CRO	Clinical Research Organization
CRT-D	Cardiac Resynchronization Therapy Defibrillator
CV	Curriculum Vitae
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
EHRA	European Heart Rhythm Association
ENF	Event Notification Form
ESC	European Society of Cardiology
FDA	US Food and Drug Administration (http://www.fda.gov/)
FPI	First Patient In
FU	Follow-up
GCP	Good Clinical Practice
GNF	General Notification Form
h	Hour
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
IB	Investigator's Brochure
ICD	Implantable Cardioverter Defibrillator
ICE	Intracardiac Echocardiography
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)
LA	Left Atrium
LKP	Leiter der klinischen Prüfung
LPO	Last Patient Out
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
OoS	Out of Service
p.a.	per anno
PCI	Percutaneous Coronary Intervention
PID	Product ID
PDF	Portable Document Format (www.adobe.com)
PI	Principal Investigator
PM	Pacemaker
PMCF	Post Market Clincal 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
s	Second
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
SDV	Source Data Verification
sECG	subcutaneous Electrocardiogram
StdDev	Standard Deviation
STEMI	ST Segment Elevation Myocardial Infarction
TIA	Transient Ischemic Attack
USADE	Unanticipated Serious Adverse Device Effect
USB	Universal Serial Bus

V	Volt
VF	Ventricular Fibrillation
VT	Ventricular Tachycardia
WHO	World Health Organization

2 SYNOPSIS

Title:	**BIO** monitorin**G** in patients with preserved left ventric**U**lar function **A**fte**R** **D**iagnosed **M**yocardial **I**nfarction Study acronym: BIO|GUARD-MI study
Patient collective:	Patients with a history of 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 (including USA)
Investigational device(s)	BioMonitor or successors
Accessory components to Investigational device(s)	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 patient will decrease the risk to experience a MACE in patients with a history of MI, CHA_2DS_2-VASc-Score ≥ 4 in men / ≥ 5 in women and LVEF > 35 %.
Primary endpoint:	Time to first MACE
Secondary Objectives:	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:	<u>To assess the time to</u> • 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 <u>To assess the time to first</u> • Atrial fibrillation • Atrial flutter • Non-sustained VT • Sustained VT • Sinus arrest • Sinus bradycardia • 2,3rd degree AV block or advanced AV block <u>To assess the quality of life</u> • 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.
Inclusion criteria	• Patient has a history of MI according to guidelines • CHA_2DS_2-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[1] clinical investigation is allowed • Age < 18 years • Woman who are pregnant or breast feeding
Study duration:	Patients are randomized (device yes/no) 1:1. 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 they complete their final study termination visit or the sponsor determines a premature study termination after consultation with the DSMB and Steering Committee. Estimation of total study duration: 74 months First Patient In actual: August 2015 Last Patient Out targeted: ~October 2021

[1] Following the definition of the European clinical trial directive 2001/20/EC, 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 andepidemiological methods shall be used for the analysis of collected data.

Follow-up scheme:

Enrollment/Baseline

- Verification of inclusion/exclusion criteria
- Patient 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

(time of implantation: as soon as possible but at latest 8 weeks after enrollment)

- Implantation of the BioMonitor
- Programming of the BioMonitor
- Adverse events
- Final patient instruction on investigational device

Discharge

(visit window not specified)

- Final patient instruction on study course
- Cardiovascular medication and non-cardiovascular medication
- Lab parameters
- Adverse events

Follow-up

- No pre-planned in-hospital follow-up visits

  Unplanned visits (patient- 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)

	Final Study Termination Visit • Final subject contact at the site • Document whether the study termination was regular or premature and if applicable the reason for a premature termination • Adverse events
Coordinating Clinical Investigator	[redacted]
Boards and Committees	• Central Electrocardiogram Monitoring Board • Data Safety Monitoring Board • Endpoint and Adverse Event Committee • Steering Committee • Publication Steering Committee
Sponsor	BIOTRONIK SE & Co. KG Woermannkehre 1 12359 Berlin Germany
Local Sponsor U.S.	BIOTRONIK, Inc. Clinical Studies Department 6024 Jean Road Lake Oswego, Oregon 97035 USA

3 INTRODUCTION

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) 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-MI 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 MI. 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 normo-frequent 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 severly 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 MI [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, also 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.

The BIO|GUARD-MI study therefore aims to investigate whether continuous arrhythmia monitoring and detection, using an ICM (BioMonitor) in patients after MI with LVEF > 35 % but other cardiovascular risk factors, decreases the risk of MACE if patients are appropriately examined and treated for the observed arrhythmias.

4 INVESTIGATIONAL DEVICE

4.1 Summary description of the investigational device and its intended purpose

Investigational device: BioMonitor or CE-approved successor.

The BioMonitor is an ICM used to automatically detect and record episodes of arrhythmia in patients at risk for bradycardia, tachycardia, asystole and AF. The ICM is not intended to deliver any therapy.

The device reports the recorded episodes and the related statistical data via a physician's programmer and telemetrically via BIOTRONIK Home Monitoring®.

4.2 Manufacturer

The manufacturer of the BioMonitor is the sponsor of the study:

BIOTRONIK SE & Co. KG
Woermannkehre 1
D – 12359 Berlin
Germany
www.biotronik.com

4.3 Model name including software version and accessories

Devices undergoing clinical investigation:

- BioMonitor or CE-approved successor

Participating sites located outside the CE area use the devices after market or study approval by the respective regulatory institution according to national regulations.

The device under investigation is to be used with the following components:

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

Patients 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 CE-approved successor

Patients who are receiving the investigational device may be provided with a CE approved 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.

4.4 Description of traceability

Each BioMonitor, CardioMessenger or Remote Assistant has an 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 clinical study data base.

4.5 Intended purpose and patient population of the device in the study

The BioMonitor will be used according to its intended and regulatory approved use as outlined in the technical manual. In short, the primary purpose of the BioMonitor is to provide early detection and diagnostics of symptoms of cardiac arrhythmias, which can be manifested clinically. The BioMonitor is indicated in patients with an increased risk for cardiac arrhythmias.

The population selected for this clinical investigation is expected to have an increased risk of cardiac arrhythmias. Consequently, the BioMonitor will be used to facilitate an early diagnosis and treatment of cardiac arrhythmias and to prevent a potentially fatal disease progression.

4.6 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, or bradycardia.

4.6.1 BIOTRONIK Home Monitoring® with daily sECGs

The BioMonitor has the ability to transmit data over a distance of several meters using bi-directional long-range telemetry, i.e. without the need of a wand. The data are transmitted to a patient device (CardioMessenger) that is placed a few meters away from the patient. In case automatically detected arrhythmias occurred, the BioMonitor is able to transfer sECGs with a priority ranking which arrhythmia will be sent in accordance with the technical manual. Via mobile phone technology, the CardioMessenger forwards the data to the Home Monitoring Service Center (HMSC). The data received by the Service Center are arranged in graphs and tables in the form of a CardioReport and can be viewed by the physician on a secure internet platform. In this study a Central Electrocardiogram Monitoring Board (CEMB 9.8.5) will be installed to ensure a centralized arrhythmia adjudication process and consequent forwarding to the study sites in case of relevant arrhythmia episodes.

4.7 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.

4.7.1 Description of medical and surgical procedures

The BioMonitor has to be implanted by a physician in accordance with the standard implantation procedure. 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’.

5 JUSTIFICATION FOR THE DESIGN OF THE CLINICAL INVESTIGATION

5.1 Pre-clinical data

To study the feasibility and several features of the BioMonitor, acute and chronic animal studies in Yucatan pigs have already been performed. There were good results without any conspicuousness.

5.2 Clinical data

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

5.2.1.1 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.

5.2.1.2 BioMonitor Master Study

The objective of the Master Study of the BioMonitor was to confirm the safety and efficacy of the ICM to collect post market clinical follow up (PMCF) data. The data of 153 patients, enrolled in 17 clinical sites in 6 countries including Germany and Denmark, were included in the interim report [29] that was submitted to the respective competent authorities (CA). The final report did confirm the results of the interim report [2].

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.

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

No BioMonitor related SADE up to the 3 month follow-up has been 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 a rate of 93.5%. Only 5 patients provided a QRS-detection positive predicted value (PPV) smaller than 90% (Min 85.5%).

Hence, as presented in the interim report, the ICM BioMonitor is considered to be safe and efficacious [29].

5.2.1.3 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.

5.2.1.4 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 though the 90-day follow-up visit that require additional invasive intervention to resolve. 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 show 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.

5.2.2 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 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 today 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;30]. 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 [31-34].

5.3 Justification of the design

Pre-clinical as well as clinical data did confirm the ICM BioMonitor to be safe and efficacious.

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, patients will be enrolled, randomized (50 % of the patients will be implanted with the BioMonitor; see section 8.2.1) 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 investigated 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-hospital visits other than the study termination visit are part of the study. However, treatment recommendations 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 patient 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 patients will be contacted directly via telephone at regular intervals.

6 RISKS AND BENEFITS OF THE DEVICE AND CLINICAL INVESTIGATION

6.1 Anticipated clinical benefits

6.1.1 Benefits for patients randomized to the BioMonitor group

As a result of ICM implantation, the heart rhythm of study patients 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 patient that has caused the arrhythmia.

6.1.2 Benefits for patients randomized to the control (non-BioMonitor) group

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

6.1.3 Benefits for future patients

If the study will be successful, it may show that patients 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 patients. 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.

6.2 Anticipated risks

6.2.1 Anticipated adverse device effects

ICMs are implanted in a subcutaneous position and thus require an invasive implantation procedure. Please see Table 1 with 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 1: Surgical Risks

Frequency	Percentage (%)	Risk
Frequent 1 to 10 patients out of 100	Up to 3[35-38]	local infection at insertion site
	Up to 3[36]	superficial infection at insertion site
	Up to 1,9[38]	irritation or inflammation at insertions site
	Up to 1,2[35]	local erosion at insertion site
	Up to 1,5[36]	erythema at insertion site
	Up to 1,5[35-38]	persistent pain at inframammary implant site
	Up to 3[37]	difficulties at device interrogation
	Up to 5[37]	device migration
	Up to 2,3[35;37]	device repositioning
	Up to 2,4[35-38]	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 [39;40].

The safety of ICMs has been investigated in many studies with regards to syncope and AF management [41]. It has been demonstrated successfully that the strategy of prolonged monitoring in patients with Cardiac Implantable Electronic Devices (CIED) is safe [42].

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 1.

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 patients and take corrective actions during an in-hospital visit, i.e. re-programming of the device settings.

6.2.2 Residual risks associated with the device

Despite all measures to control the risk (see section 6.3), a residual risk remains.

6.2.3 Risk associated with participation in the study

Apart from the anticipated adverse device effects discussed in section 6.2.1, 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 patient 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.

6.2.4 Possible interactions with concomitant medical treatments

No interactions with concomitant medication or medical treatment are expected.

6.3 Steps to control or mitigate the risks

Risks associated with the BioMonitor (see section 6.2) 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 patient'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 CIP in all aspects and to promptly supply BIOTRONIK with all pertinent information required by this CIP.

There are no known contraindications. However, the particular patient's state of health determines whether a subcutaneous device will be tolerated long term.

6.4 Risk-to-benefit rationale

The investigational device is approved in Europe for standard medical care (CE mark). In countries located outside the CE area, devices will only be implanted after market or study approval of the responsible regulatory institution. Being expected at increased risk for cardiac arrhythmias, the patient population to be enrolled in this clinical study has an indication for implantation of the investigational device according to the technical manual. Nevertheless, in most cases this will not be clinical routine at the study sites.

It is not anticipated that the patients participating in this study are exposed to any risks beyond those stated in section 6.2.1. 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.

7 OBJECTIVES AND HYPOTHESES

7.1 Objectives

7.1.1 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 patient will decrease the risk to experience a MACE in patients with a history of MI, CHA_2DS_2-VASc-Score ≥ 4 in men / ≥ 5 in women and LVEF > 35 %.

See section 8.3.1 for the definition of MACE.

7.1.2 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.

7.1.3 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.

7.1.3.1 All-cause mortality

The occurrence of death for any cause will be recorded and analyzed.

7.1.3.2 Cardiovascular death

The occurrence of cardiovascular death will be recorded and analyzed.

7.1.3.3 Worsening of the patient status due to heart failure

The occurrence of worsening of the patient status due to heart failure requiring hospitalization or urgent visit will be recorded and analyzed.

7.1.3.4 Hospitalization resulting from arrhythmia

The occurrence of hospitalization resulting from arrhythmia will be recorded and analyzed.

7.1.3.5 Hospitalization resulting from acute coronary syndrome

The occurrence of hospitalization resulting from acute coronary syndrome will be recorded and analyzed.

7.1.3.6 Hospitalization or death resulting from stroke

The occurrence of hospitalization or death resulting from stroke will be recorded and analyzed.

7.1.3.7 Major bleeding requiring hospitalization

The occurrence of major bleeding requiring hospitalization will be recorded and analyzed.

7.1.3.8 Systemic embolism requiring hospitalization

The occurrence of systemic embolism requiring hospitalization will be recorded and analyzed.

7.1.3.9 Arrhythmias

The occurrence of arrhythmias will be recorded and analyzed independently of whether a consequent therapy is indicated.

7.1.3.10 Type of initiated therapies

It will be evaluated which diagnoses will be made and which therapies will be initiated, based on ICM-detected arrhythmias.

7.1.3.11 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.

7.1.3.12 Quality of Life (QoL)

The investigation of the patients' quality of life is not intended to show a benefit by the implantation of the ICM, but to exclude that the implantation or the monitoring of patients has a negative impact on their well-being.

7.2 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. More detailed information about the endpoints is provided in section 8.3:

H_0: Null hypothesis: $H_0 : HR \geq 1$
which means that monitoring patients of the BioMonitor group will *not* lead to a longer time-to-first-event of MACE compared to the control group.

H_A: Alternative hypothesis: $H_A : HR < 1$
which means that monitoring patients of the BioMonitor group will lead to a longer time-to-first-event of MACE compared to the control group.

It is expected that there is a HR < 1 in favour 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.

7.3 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 patients of the BioMonitor group will *not* lead to a shorter time to first arrhythmia that requires guideline-recommended therapy, in the BioMonitor group compared to the control group.

H_A: Alternative hypothesis: $H_A : HR > 1$
which means that monitoring patients of the BioMonitor group will lead to a shorter time to first arrhythmia that requires guideline-recommended therapy compared to 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).

7.4 Safety assessments

The safety assessments are already covered by the primary and secondary objectives. The occurrence of all AEs during study participation is documented and assessed (see section 18) and will be evaluated with regards to the primary and secondary objectives.

8 DESIGN OF THE CLINICAL INVESTIGATION

8.1 General considerations

The BIO|GUARD-MI study is a multicenter, prospective, randomized (1:1), controlled, parallel-group, open, international study (including USA) with an event-driven design. The study is operatively divided into 2 phases. In the first phase 640 patients will be enrolled within approximately 2 years after FPI. After 600 patient years of cumulative follow-up have been collected, a blinded analysis will be performed to assess the primary endpoint rate. Based on the assessed rate (see section 11.7), the study will enter the second phase or be discontinued prematurely. This is necessary because it is impossible to obtain solid estimates of the endpoint rates for the included population from the literature. In case of a too low endpoint rate, the study could be expected to fail in its primary objective, even if the BioMonitor group had a much reduced endpoint rate.

In the second phase enrollment will continue in the same way, but in more investigational sites than the first phase, and without interception until up to 2900 patients entered the study. The duration of the second study phase is estimated to last 4 years but ultimately is dependent on when the number of needed endpoints for the final analysis is reached. In the second phase US patients will contribute to the study.

As a result of the specific national requirements in the U.S., a U.S.-specific amended protocol is valid for U.S. sites. Differences compared to this Clinical Investigation Plan are displayed in section 23.1.

The study includes an enrollment-assessment and randomization procedure. The randomization is 1:1, either in the BioMonitor group (patients are implanted with the BioMonitor) or in the control group (patients 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 patients randomized to the BioMonitor group, the implantation shall be performed as soon as possible but at latest 8 weeks after enrollment. Most study procedures will typically take place during the index hospitalization[3] (enrollment, implantation if applicable and discharge).

Following discharge, patients will be treated according to clinical routine/guidelines. Hence, no study specific pre-planned procedures will be performed. The patients will be encouraged to contact their general practitioner or cardiologist regularly, as it is clinical practice in the investigational site, or in case of symptoms or malaise. The primary or secondary care provider will be suggested to transfer the patient to the investigational site only if tertiary level care will be required.

To assess the primary endpoint, all patients 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 patient will receive no medical advice of any kind but will only be asked about events of the preceding period (see section 9.6).

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

Additionally, patients 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 patient is dependent on the time of entry into the study. All patients will be followed until a final study termination visit has been completed or the sponsor determines a premature study termination after consultation with the DSMB and Steering Committee.

The study is designed to test the primary hypothesis defined in section 7.2 based on the composite endpoint defined in section 8.3.

8.2 Measures taken to minimize or avoid bias

8.2.1 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 patients included are assumed to be at increased risk for MACE. However, currently it is unknown which patients 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 patients of the BioMonitor group and Control group, the randomization date is defined as the discharge from the index hospitalization.

8.2.2 Blinding

The investigator can't be blinded because diagnostic information from the ICM has to be used. The blinding of the patient 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.

8.2.3 Other

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

- Patient selection according to pre-defined inclusion and exclusion criteria.
- It is the intention of the study design that all patients will be followed-up and treated in accordance with clinical routine/guidelines. Nevertheless, to gather endpoint information all patients will be contacted via telephone on a 6 monthly basis (see section 9.6).
- In case of Home Monitoring findings, patients 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 follow-up (see

section 9.6) 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 patients during the telephone follow-up calls.

- Standardized procedures/processes for (see section 9):
  - Standardized telephone procedures outlined in a separate telephone manual
  - Standardized methods for data collection, including the documentation of potential confounding factors, such as patient demographics, medical history and procedural parameters
  - Standardized procedures for BioMonitor implantation in accordance with the technical manual
- Formation of a Publication Steering Committee (see section 21).
- Formation of an Endpoint and Adverse Event Committee (EAEC) that will assess all cardiovascular SAEs and all cases of patient death in a blinded and standardized manner regarding the primary endpoint (see section 9.8.1).
- A CEMB will be formed to ensure a standardized interpretation of the Home Monitoring findings and consequent forwarding to the study sites (see section 9.8.5).

8.2.4 Final Study Termination Visit

All active patients will be asked to visit the study site for a final study termination visit. After a complete medical record review for adverse events, the investigator will interview the patient about any adverse events that occurred during study participation. Additional information about adverse events may be obtained from family members, primary care providers or other hospitals where care was provided.

8.3 Endpoints

8.3.1 Primary endpoint

The primary endpoint is the time from randomization (definition see section 8.2.1) to the first MACE during the clinical investigation. Patients 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. Patients who reach the primary endpoint will continue to be followed up until the formal termination of the study is announced (see section 8.1).

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[4]

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

[4] Like for other endpoints, scientifically accepted definitions will be used also for this endpoint and will be included in the EAEC board charter [see Hicks et al, JACC (2015);66:403-69].

- Arrhythmia
- Acute coronary syndrome
- Stroke
- Major bleeding
- Systemic embolism

8.3.1.1 Endpoint assessment definitions

A further specification of the endpoint adjudication process will be given by the experts of the EAEC (see section 9.8.1) 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 patients 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 (see section 9.6). 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 patient death will be evaluated by a blinded central Endpoint and Adverse Event Committee (EAEC, see section 9.8.1) and assessed with respect to the definition of the primary endpoint.

8.3.2 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. Patients 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.

8.3.3 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 patients 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.

8.3.3.1 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.

8.3.3.2 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 (see section 9.8.1) and documented in a separate charter agreement.

8.3.3.3 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 patient 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.

8.3.3.4 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.

8.3.3.5 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.

8.3.3.6 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.

8.3.3.7 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.

8.3.3.8 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.

8.3.3.9 Time to first arrhythmia

Assessment of the time from randomization to first arrhythmia.

8.3.3.10 Type of initiated therapies

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

8.3.3.11 Time to first therapy

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

8.3.3.12 Quality of Life (QoL)

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

8.4 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.

8.4.1 CRF 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 2 provides an overview of eCRFs and procedures.

Data collected during study initiation and termination

- Enrollment CRF
- Baseline CRF
- Implantation CRF
- Discharge CRF
- Termination visit CRF
- Study termination CRF
- Elective Replacement Indicator (ERI) form
- Remote Assistant form
- Protocol deviation / Protocol non-compliance CRF

Data collected due to adverse events (AE)

- Adverse event CRF
- Concomitant medication log eCRF, required only if AE is suspected to be due to a medication
- Device deficiency (DD) CRF

Data collected by the CRO performing the telephone follow-up

- Telephone follow-up questionnaire (see section 9.6)
- Quality of life questionnaires (see section 9.6)

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

- Arrhythmia notification form (see section 9.5)
- General notification form (see section 9.5)
- IHF event notification form (see section 9.5)

Table 2: Overview CRFs and Investigations

Investigation	Enrollment	Baseline	Implantation	Discharge	Telephone contacts (every 6 months)	Arrhythmia notification form	General notification form	IHF notification form	Termination
Patient informed consent	x								
Verification of in- and exclusion criteria	x								
Patient demographics		x							
NYHA class		x							x
Echo parameters		x							
Specification of MI	x								
Medical history/Co-morbidities		x							
Cardiovascular medication				x					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 patient						x	x	x	
Patient interview						x	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

8.4.1.1 Enrollment Form

The following information will be documented in the Enrollment Form:

- Confirmation that patient has provided written informed consent
- Verification of inclusion and exclusion criteria
- Specification of MI

8.4.1.2 Baseline Form

The following information will be documented separately in the Baseline Form due to a possible timely delay to the actual enrollment of the patient:

- Result of the randomization
- Demographic information
- Echocardiographical data
- 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, medical conditions
- Occurrence of AEs after written informed consent has been provided
- Scheduling implantation of the Implantable Cardiac Monitor and/or discharge

8.4.1.3 Implantation Form

The implantation of the BioMonitor is 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 implantation or exchange
- Interrogation and programming details
- Home Monitoring (verification that CardioMessenger was handed out to the patient; documentation of serial number, general patient instruction on the use of the CardioMessenger)
- Occurrence of AEs since baseline

8.4.1.4 Discharge Form

Any actions taken or initiated since the implantation are documented on the Discharge Form. The patient will be reminded about general study aspects and will be educated when and how to seek medical attention. The latest status with regards to the patient's cardiovascular medication and general lab parameters will be documented. The following information will be documented in the Discharge Form:

- Actions taken or initiated at discharge
- General patient instructions on the study course (telephone follow-up, etc)
- Documentation of cardiovascular and non-cardiovascular medication
- 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
    - For other lab parameters the most currently estimated value should be collected (not older than 2 months before data of discharge)
- Occurrence of AEs / DDs since baseline / implantation

8.4.1.5 Adverse events

Adverse event reporting starts with the patient signing the Patient Informed Consent Form. The responsible investigator has to evaluate and report any AE that is brought to his 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 in section 18.8.

8.4.1.6 Device deficiency

Device deficiencies (DD) of the BioMonitor will be reported and documented. DDs are defined by the ISO 14155. Investigators have to adhere to notification timelines as outlined in section 18.8.

8.4.1.7 ERI form

Devices will be explanted according to physician judgment, at the end of battery life or for medical reasons. The ERI form will only be completed when the battery of the investigational device has reached end of life. In case of explantations due to medical reasons, e.g. patient death or implantation of a pacemaker, the reason for explantation will be documented on the respective Adverse Event form.

In case of death the BioMonitor should be interrogated prior to the explantation procedure, if possible. If not possible, it is important that the BioMonitor is explanted, and sent to the implanting center for interrogation. 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).

8.4.1.8 Study termination Forms

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

In case of regular study termination, information on planning, completion, and outcome of the required actions (as outlined in section 8.2.4) to ensure accurate AE reporting is documented in the additional termination visit form.

8.4.1.9 Further eCRFs and forms

Further eCRFs and forms referring to the data collected by the CRO performing the telephone follow-up and data resulting from Home Monitoring messages and other medical events requiring tertiary level care will be considered in section 9 of this protocol.

8.5 Device replacement or explantation

8.5.1 Device replacement

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 patient'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 patient shall remain in the study, independent of the decision to replace the device or not.

8.5.2 Device explantation

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 patient the investigator is free to monitor the patient even after her or his official termination from the study.

8.6 Equipment to be used for the assessment of variables

No other equipment will be specifically required for the conduct of this study next to the devices listed in section 4.3.

8.7 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.

8.8 Used devices and comparators

Half of the randomized patients will be implanted with the BioMonitor. No comparator system or specific study related medication will be used during this investigation.

8.9 Subjects

The investigator is responsible for screening all potential patients and selecting those who are appropriate for study inclusion. Every investigator can enroll as many patients as desired until the sample size for the entire study has been reached. End of patient enrollment is announced by the clinical project manager.

8.9.1 Description of patient collective

Patients meeting the inclusion criteria and none of the exclusion criteria will be enrolled in the study. According to the sample size calculation (see section 11.2), up to 2900 patients will be enrolled into the study including 5 % drop-outs per year. The patient number is based on an expected endpoint-rate (see section 11.2) required to reach the study goal of 372 patients with one or more endpoint events. However, patient number will automatically be adapted in case the actual endpoint rate deviates from the expected rate. Thereby the limited number of patients to be excluded from the analysis set (see section 11.1.2) is not considered.

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

- BioMonitor group (best medical care and implanted with BioMonitor)
- Control group (best medical care)

By defining a termination visit (see section 8.2.4), the study protocol deviates from the initial planning with a defined number of primary endpoints.

8.9.2 Inclusion criteria

The following inclusion criteria **must be met** to enroll a patient in this study:

1. Patient has a history of MI according to guidelines
2. CHA_2DS_2-VASc-Score ≥ 4 in men / ≥ 5 in women (see section 8.9.2.1)
3. LVEF > 35 % as estimated within 6 months before enrollment but after conclusion of AMI treatment
4. Patient accepts activation of Home Monitoring
5. Patient is able to understand the nature of the clinical study and has provided written informed consent

8.9.2.1 Definition of CHA_2DS_2-VASc-Score

CHA_2DS_2-VASc acronym[5]	**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	+1

[5] 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS, (European Heart Journal, doi:10.1093/eurheartj/ehw210)

• Fasting glucose >125 mg/dL (7 mmol/L) or treatment with oral hypoglycaemic agent and/or insulin	
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

8.9.3 Exclusion criteria

The following exclusion criteria **must not be met** to enroll a patient in this study:

1. Patients with hemorrhagic diathesis
2. Permanent oral anticoagulation treatment for atrial fibrillation
3. Indication for chronic renal dialysis
4. Pacemaker or ICD implanted or indication for implantation
5. Parkinson's disease
6. Life expectancy < 1 year
7. Participation in another interventional clinical investigation during the course of the study, i.e. the participation in a non-interventional[6] clinical investigation is allowed.
8. Age < 18 years
9. Woman who are pregnant or breast feeding

8.9.4 Drop-out criteria

8.9.4.1 General

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

Once a subject is enrolled and successfully implanted in case 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:

- Patient death (see section 8.9.4.2)

[6] Following the definition of the European clinical trial directive 2001/20/EC, 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 andepidemiological methods shall be used for the analysis of collected data.

- Withdrawal of patient consent (see section 8.9.4.3)
- Loss to follow-up (see section 8.9.4.4)
- Early discovery of a violation of inclusion or exclusion criteria (see section 8.9.4.5)
- Investigator initiated drop-out (see section 8.9.4.6)

Applying the intention-to-treat (ITT) principle, patients considered to be drop-outs are not excluded from the analysis set, except if the conditions described in section 11.1.2 are fulfilled.

8.9.4.2 Patient death

In the event of subject death during study participation, personnel at the investigational site are requested to notify BIOTRONIK 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 that are explanted must be returned to BIOTRONIK for analysis.

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

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

8.9.4.3 Withdrawal of patient consent

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.

8.9.4.4 Loss to follow-up

Patients lost to follow-up are those for whom contact is lost despite the investigator's best efforts to locate the subject. Study sites should attempt to contact these subjects and all contact attempts should be documented. All efforts must be documented in the patient

record by copies of correspondence. Patient's compliance should be pursued until a definitive reason for failure to participate is determined (e.g. patient moved with no forwarding address). The investigator should also contact the CRO responsible for collecting AEs, which will support him in the attempts to locate the patient.

8.9.4.5 Early discovery of a violation of inclusion or exclusion criteria

If a patient of the BioMonitor group or Control group will be identified to violate any in- 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.

8.9.4.6 Investigator initiated drop-out

The investigator may initiate a premature study termination for legal reasons (e.g. in case of pregnancy during the course of the study) or if the study participation endangers the patient's well-being or safety. However, a member of the Steering Committee or CI must be consulted before implementation, except in cases of emergency. Since the CIP does not enforce or prohibit any treatments, it appears highly unlikely that such a case can occur.

In contrast, changes of the patient's treatment, even if related to monitoring or treatment of arrhythmias, do not justify a drop-out, since the patient's further clinical course can be recorded. Two examples are the impossibility to use HM in a new environment of the patient (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 patient, because the exclusion of such patients might introduce a bias in favour of the ICM arm.

8.9.5 Point of enrollment and study termination

The point of enrollment is the time at which a patient signs and dates the informed consent form. The informed consent process is described in section 17. Study related procedures, documentation and collection/following of adverse events will start from this day on.

Regular point of termination for the individual patient is the respective date of the final study termination visit.

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

- In case of patient 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 patient 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 patients for any primary analysis because this might introduce a bias in favor of the BM arm.
- If patient is defined as drop-out patient 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 patient for safety reasons.

8.9.6 Timelines

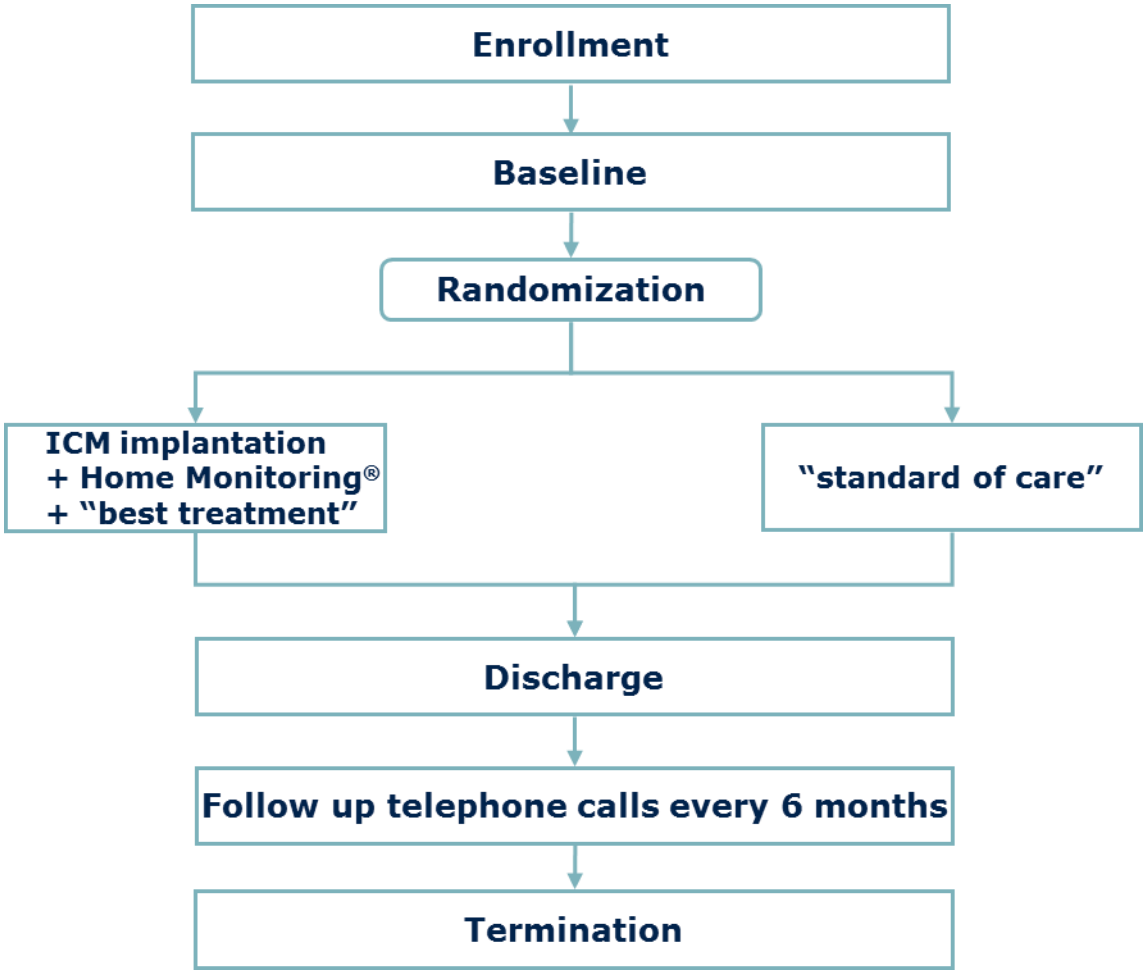
First Patient In (FPI): Aug 2015 (actual date of FPI)

Last Patient Out (LPO): ~ Oct 2021Total study duration: ~ 74 months

9 STUDY PROCEDURES

9.1 Overview

Table 3: Study Flowchart



9.2 Enrollment, Baseline and Randomization

Prior to enrollment into the clinical investigation, all patients 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 patient prior to enrollment.

All successfully enrolled patients 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 8.2.1. The randomisation code will be generated by the electronic data capture (EDC) system.

9.3 Implantation

In patients randomized to the BioMonitor group, the BioMonitor will be implanted after enrollment according to standard procedures as described in the technical manual. See section 4.7 for the summary of training and experience needs.

Mandatory 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.

Mandatory 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.

9.4 Discharge

Upon discharge from the index hospitalization [7], the patient will receive guideline recommended prescriptions and education about life-style recommendations. In addition, general study aspects such as the telephone follow-up concept will be repeatedly explained to the patient and it will be suggested how to seek medical attention. The recommendation will be to visit a general practitioner or cardiologist in case of a worsening of symptoms or the general well-being. The patient will be further advised to contact the investigational site provided that the general practitioner or cardiologist finds a condition for which it appears that the attention of a tertiary care facility is required. Hence, the patients will be discouraged from contacting the investigational site on his or her own decision but should only visit the investigational site after being advised to do so.

The patients 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, patients will be suggested to remember date and place of any hospitalization, possibly in a diary. This applies to patients of both study arms.

9.5 Home Monitoring Analysis

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

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

Home Monitoring data shall be analyzed on all working days by the CEMB (see section 9.8.5). If an arrhythmia was detected, the CEMB shall contact the investigator immediately. Parallel to informing the physician, the detected event shall be entered by the CEMB in the CDMS using the 'Arrhythmia notification form (ANF)'. For a detailed description of the CEMB-responsibilities and the respective process, a charter will be developed in collaboration with the involved stakeholders.

After evaluating the event in the HMSC, the investigator shall enter the assumed rhythm in the CDMS using the same form (ANF) 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 patient or not. Specifics about the contact and possibly resulting in-hospital visit shall be recorded in the ANF and in the adverse event form if applicable. Therefore, event triggered in-hospital 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-hospital visits, the patient may have been sent in by a primary or secondary care provider or the patient appears at the site on his own decision. For these cases, the 'General notification form' captures the reason for the visit as well as the types of examinations and therapies performed. If during in-hospital visits, the investigator is notified about adverse events, the information is entered into an AE CRF. To avoid a bias in favour 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 patient interviews (see section 9.8.6). Thus, it will be possible to estimate a possible underreporting of primary endpoints by looking separately at the information received during the telephone contacts.

9.6 Telephone follow-up

A telephone follow-up regimen will be implemented and replace in-hospital follow-up visits. To obtain endpoint related information, all patients 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 patient'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 patient
- 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.

Telephonic follow-up activities and consequent source data tracking will be performed by an external CRO contracted by the sponsor (see section 9.8.6). Detailed telephone follow-up guidelines will be provided in a separate document, the 'telephone follow-up manual'.

Since all primary endpoints constitute adverse events, the respective information received via telephone contact must be forwarded by the CRO to the respective study site and will ultimately be recorded in adverse event forms. The description of every SAE must be sufficiently documented and confirmed by source data to allow the adjudication by the EAEC.

9.7 Study Termination

The end of study participation of the individual patient will be documented in the Study Termination Form, independent of the reason for termination (see also section 8.9.5). Reasons for exclusion from the study should be documented as far as possible. All applicable eCRFs shall be completed as far as possible.

All active patients will be asked to visit the study site for a final study termination visit. After a complete patient medical record review for adverse events, the study personnel will interview the patient about any adverse events that occurred during study participation. Additional information about adverse events may be obtained from other sources, in accordance with local regulations, e.g. from family members, primary care providers or other hospitals where care was provided.

9.8 After the termination the patient's ongoing medical treatment is to the physician's discretion or should follow the clinical routine.Description of those activities performed by sponsor representative

Monitoring activities will be performed by sponsor representatives as outlined in the monitoring plan. In the US, the sponsor is assisted by US based staff, led by the Director of Clinical Studies U.S., who is responsible for all U.S.-specific issues during the course of the clinical investigation.

The sponsor might 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 9.8.1)
- Safety monitoring (see section 9.8.2)
- Overall guidance of the clinical investigation (see section 9.8.3)
- Coordination of the publication process (see section 9.8.4)
- Home Monitoring analysis (see section 9.8.5)
- Telephone follow-up activities (see section 9.8.6)

9.8.1 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 patient 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.

9.8.2 Responsibilities of the Data Safety Monitoring Board (DSMB)

The DSMB will review accumulating study data to address patient 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.

9.8.3 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 CIP 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.

9.8.4 Responsibilities of the Publication Steering Committee (PSC)

Please refer to section 21.1.

9.8.5 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 9.5). Details with regards to the specific process will be determined in the CEMB charter.

9.8.6 Responsibilities of the Contract Research Organisation (CRO)

An external service provider has been appointed to perform the telephone follow up interviews of all patients 4 weeks following enrollment and then every six months until study termination (see section 9.6). 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

In the course of the study additional service providers might be contracted depending on the countries which will be further included.

9.9 Responsibilities of the investigator

9.9.1 Responsibilities of the Principal Investigator

The following extract of responsibilities resides with the Principal Investigators (PI):

- Demonstration of suitability of the investigational site with respect to a sufficient number of patients to be recruited for the study, availability of qualified investigators, support staff and adequate facilities, required to execute the study at the investigation site.
- Communication with the ethics committee (EC). As far as appropriate and according to local regulations, the PI will maintain communication with the appropriate EC. This includes:
    - Communication to obtain a favourable opinion of the ethical committee to conduct the study.
    - Reporting of safety information and deviations from the study plan affecting the rights, safety or well-being of the patients or the scientific integrity of the study.
    - The PI shall provide the sponsor with copies of any communications between the PI and the EC pertaining to this study.

- Informed consent process as described in section 17 of this CIP and notification of that process and date in the patient record.
- Ensure that the study is conducted at the investigation site in full compliance with this CIP. This includes:
    - Confirmation to comply with the study protocol.
    - Creation and maintenance of source documents.
    - Follow the procedures with respect to study deviations as described in this CIP (see section 14).
    - Ensure the availability of an adequate investigation team and facilities.
    - Ensure accurate, complete and timely reporting of collected data to the sponsor.
    - Allow the sponsor to perform study monitoring and auditing and be accessible for the sponsor with regard to these activities.
    - Allow and support auditing activities from regulatory authorities and the ethical committee.
    - Data retention in compliance with this CIP and local regulations.
    - Safeguarding the rights of the physical and mental integrity as well as the privacy and the protection of the data of the study patients.

- Medical care of patients participating in this study, specifically including:
    - Medical care to patients during and after the patient's participation in the study in case of an adverse event and informing the patient about the nature and possible cause of the event.
    - Inform patients of any new significant findings occurring during the study.
    - Provide patients with well-defined procedures for possible study-related emergency situations and make appropriate arrangements for emergency treatment.
    - Ensure that clinical records are clearly marked to indicate that the patient is enrolled in this study.
    - Make appropriate efforts to ascertain the reason(s) for a patient to prematurely withdraw from the study, while fully respecting the patient's rights.
    - Ensure that patients of vulnerable population are not enrolled (see section 19).
- Safety reporting (see section 18), including:
    - Documentation of every adverse event and observed device deficiency, including an assessment.
    - Report adverse events and device deficiencies to the sponsor, ethical committee and regulatory authorities according to the reporting timelines defined in this CIP and in compliance with local regulations.
    - Upon the sponsor's request, provide additional safety-related information to the sponsor regarding a particular event.

- The PI has to ensure that all participating investigators (including the PI) of the corresponding site are adequately qualified. Qualification will be verified by the Sponsor. Note, depending on the local regulations it may be necessary to submit evidence of the qualification to the responsible EC or the CA.
- The principle investigator shall provide the necessary documents to the sponsor in particular:
    - PI's CV (current, signed and dated)
    - CV of key members of the investigation team (current, signed and dated) and others who materially contribute to the study
    - GCP and/or ISO certificates of the investigation team, depending on the local requirements
    - Site responsibility log and training log
    - Ethics committee notification, correspondence and approval
    - Signed contract between the principle investigator and the sponsor
    - Investigator statement (signed and dated)
    - User and Training Log EDC System
    - Signed CIP
    - Notification to / approval from CA if applicable

9.9.2 Responsibilities of the coordinating investigator (CI) and in Germany "Leiter klinische Prüfung" (LKP)

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
- Support of reporting to CA, if applicable
- Signature of Clinical Investigation Plan (CIP) and Clinical Investigation Report (CIR)

10 MONITORING PLAN

The responsibility of BIOTRONIK SE & Co.KG as sponsor and BIOTRONIK Inc. as local sponsor in the U.S. is to ensure protocol and regulatory compliance through proper monitoring of the study.

BIOTRONIK is required to ensure that the BioMonitor is used under the immediate direction of an investigator. As the investigator, the physician is responsible for conducting the study in accordance with the signed clinical investigation agreement, the study protocol, applicable laws, and FDA and/or local regulations (e.g. 21 CFR, parts 50, 54, 56, and 812, ISO 14155, Declaration of Helsinki) and any conditions of approval imposed by the reviewing IRB/EC.

A monitor (authorized BIOTRONIK personnel, Clinical Research Associates (CRAs)/Monitor, or by authorized BIOTRONIK designees) will visit the study site periodically during the study. All participating sites will be monitored during the course of the study with visits occurring as frequently as deemed necessary to ascertain adherence to the protocol procedures, as well as maintenance of the highest data quality. A detailed monitoring plan developed by BIOTRONIK will be followed.

The entries in the electronic eCRF will be reviewed and source data verified at the investigational site by monitors as specified in the monitoring plan to ensure that the investigator and the clinical investigation team conducts the clinical investigation in accordance with the CIP, Declaration of Helsinki, ISO 14155 or ICH-GCP (U.S. sites), 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.

Periodic monitoring visits will assure, amongst others, that the facilities are still performing well; that the CIP is being followed, that the EC/IRB/CA has been informed about approved CIP 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 and the authorities, and that the investigator is carrying out all agreed activities.

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

1. Completion and submission of the required eCRFs including source data verification (SDV) and data plausibility checks
2. Completion and submission of other applicable study documentation
3. Continued acceptability of the facilities, including storage and maintenance of investigational inventory
4. Adherence to reporting timelines for adverse events
5. Adherence to the CIP
6. Adherence to ISO 14155 or ICH-GCP (for U.S. sites) and applicable FDA and 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 study management.

BIOTRONIK will evaluate the non-compliance and issue corrective actions, discontinue enrollment or as a last measure close the clinical investigation site (see section 14.4)

The investigators are obliged to provide adequate access to the original patient records and other relevant source data related to the clinical study. Adequate manned and spatial resources have to be provided for all monitoring activities. The investigational sites are asked to collaborate closely with the clinical monitor. The investigational sites are obliged to keep the source data (e.g. patient records) and CRF-entries up-to-date to ensure efficient and time-saving monitoring.

Agreement to monitoring activities was obtained from the patient in the ICF. Detailed monitoring activities and monitor responsibilities are listed in the monitoring plan.

11 STATISTICAL CONSIDERATIONS

11.1 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.

11.1.1 Statistical design

According to the original statistical planning, the study was 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 [43]. This strategy is replaced with a single final analysis of all data after study termination.

The first interim analysis has been performed. The planned second interim analysis will not be done. Due to the O'Brien Fleming design with a very low alpha_1 = 0.00025 for the first interim analysis, an adjusted significance level for the final analysis alpha_final = 0.02476 will maintain the global 1-sided significance level alpha = 0.025.

11.1.2 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 patients 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 analysed 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 patients will be excluded from the analysis set

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

11.1.3 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 patients 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

- Patients with violation of in- or exclusion criteria at enrollment
- Patients with major deviations from the CIP in accordance with the definition given in section 14.1
- Patients of the BioMonitor group without implanted device or drop-out less than 1 month after implantation
- Patients 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 violations as defined in section 14.1

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.

11.1.4 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: A one-sided log rank test is performed in the context of a confirmatory analysis of the primary hypothesis at the 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.

11.2 Sample size

The original planning assumed that 372 primary events would be required to accept the primary alternative hypothesis with 80% statistical power given an assumed hazard ratio in the population of 0.7452, and the study was to be terminated after this number of endpoints had been collected.

Instead, it was decided to enter the termination phase without any avoidable further delay. Therefore, the intended number of endpoints may not be reached.

11.3 Level of significance and the power of the study

The global significance level of the 1-sided hypothesis is 2.5%.

A statistical power of the final analysis of 80% was used for sample size calculation.

11.4 Expected drop-out rate

A drop-out of 5% of the patients per year is expected. Thereby the limited number of patients to be excluded from the analysis set (see section 11.1.2) is not considered.

11.5 Pass/fail criteria

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

11.6 Provision for an interim analysis

After the first phase, a blinded analysis of the total endpoint rate is planned. Because the blinding is not broken, this is not considered as an interim analysis. One interim analysis has been done, but no further interim analysis will be conducted.

11.7 Termination criteria

There is a blinded evaluation of the MACE rates after the event-check, which is no interim analysis because no therapy effect is investigated.

If the total number of patients with at least one MACE in both groups is less than 20 patients per 600 patient-years at the end of the event-check phase, the study will be terminated.

Furthermore, 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 after the first 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 value $\alpha_{interim1}$ = 0.00025..

11.8 Procedures for reporting of deviations to the statistical plan

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

An SAP version 1.0 was written as a separate document before 1st patient-in including a more technical and detailed elaboration of the statistical considerations as described here.

The SAP is reviewed and possibly updated based on a blind review of the data before breaking the blind for the interim analysis or the final analysis.

11.9 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

11.10 Procedure for accounting of all data for analysis

Data to be analysed 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 analysed with common statistical software packages, e.g. SAS Version 9.4 .

11.11 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 analyses are minimized and limited to baseline information which can be obtained without any additional burden for the patient. 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.

11.12 Exclusion of data from confirmatory data analysis

Details with regards to the exclusion of data from confirmatory data analysis are provided in section 11.1.2.

11.13 Minimum and maximum number of patients per site

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

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

12 DATA MANAGEMENT

12.1 Data protection

According corresponding national laws, the patient (or his or her legal representative) must declare in the ICF that he or she agrees to the recording of his or her medical data and their transfer to the sponsor, the supporting CRO IHF and, if necessary, to responsible EC and CA. The patient agrees that authorized personnel of the sponsor and the involved EC or CA (if applicable) may gain insight in the patient record to ensure that the patient was adequately informed about the clinical trial and that the CIP was followed properly.

All patient-related data and information received from the clinical study will be handled confidentially. The collected data will be pseudonymized, without using patient initials, date of birth or other privacy data, to ensure traceability of data, but preventing unauthorized identification of individual patients. The data will be transmitted to the sponsor and if necessary, to the supporting CRO IHF for electronic data handling, safety reporting and analysis in compliance with the data protection law. Insight will be given to responsible EC and CA upon request.

All involved parties are bound to data secrecy according to the national data protection law. All patients will be informed on all relevant regulations concerning data secrecy and data protection which are applicable for BIO|GUARD-MI in the ICF. Specifically, patients will be educated about their rights concerning data access, data correction, and data deletion according to applicable legislation.

The patient identification log sheet, in which the patient ID code, name, date of birth, serial number of the BioMonitor and date of informed consent is entered, will remain at the investigational sites.

The Patient Contact Form containing patient ID code, contact data, name and date of birth will be sent to the telephone follow-up provider (IHF) and archived there.

No copies of the patient identification log sheet or Patient Contact Form will be provided to the sponsor. The patients will be informed on the fact that exact identification of the patient is only possible for the investigator and the telephone follow-up provider (IHF).

12.2 Data collection

All study-relevant patient data will be documented pseudonymously in eCRF. The established Clinical Data Management System (CDMS) 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, 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 patient or new patient data into the system.

For the majority of the CRF entries source data needs to be maintained at the site and will be collected in adequate files (e.g. patient files). The data have to be stored and shall be made available upon request in order to allow SDV. Exceptions for which the CRF entry can be regarded as source data are indicated in the monitoring plan.

12.3 Procedures used for data review, CDMS cleaning, and issuing and resolving data queries

After data entry into the CDMS, 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 (CDMS) 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 CDMS 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.

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

The CDMS is hosted on a dedicated database server at the vendor MedNet Solutions, Inc. Only authorized users with fixed roles have access to the CDMS. The access is controlled and maintained by the Clinical Data Management of BIOTRONIK. Every access is automatically logged and changes of the clinical data are stored in independent audit trails. The CDMS 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 BIOTRONIK 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.

12.5 Data retention and archiving

All study related electronic documents are stored in the archive of BIOTRONIK which provides storage conditions free from risk of fire, flood, theft and vermin. The access to the files is controlled.

After CDMS closure, all eCRF data, the audit trail and other relevant CDMS content are exported and stored electronically for at least 15 years on the 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 must be deleted.

All relevant study related documents have to be stored in the Investigator's File. Documents containing patient's data, raw data and other study related documents have to be archived in the investigational site. In case of electronic source data (e.g. electronic patient records) adequate actions have to be taken to ensure data availability during the whole archiving period. All documents have to be archived by CCR and supporting CRO IHF for at least 15 years or even longer if indicated by the national legal requirements.

13 AMENDMENT PROCEDURES

If throughout the course of the study changes to the CIP are deemed to be necessary, a change justification has to be prepared which includes the rationale and content of the adjustment. The modification of the CIP can either be summarized in a separate document as an attachment to the current applicable version of the CIP or result in a new version of the CIP.

If the changes have impact on study related procedures or data analysis, they are substantial by definition.

New versions of the CIP or substantial amendments have to be reviewed and confirmed by the Coordinating Clinical Investigator and the Steering Committee. All investigators have to acknowledge the receipt of an amendment by signing an amendment agreement form.

Before implementation of any changes, substantial amendments have to be approved by the EC and – if applicable – by the CA. Non substantial amendments are submitted for notification only.

The investigator should not implement any deviation from or changes to the CIP without agreement of the sponsor and prior review and documented approval from the EC (and CA if required). The only exception is the necessity to eliminate an immediate hazard to the subjects, or when the change involves only logistical or administrative aspects of the study.

14 DEVIATIONS FROM CLINICAL INVESTIGATION PLAN

14.1 CIP compliance and exceptions

All sponsor personnel, all investigational site personnel as well as other third parties, who are involved in tasks covered by this CIP, are generally obliged to comply with this CIP. A U.S.-specific amendment is available for investigational sites in the U.S. to better address U.S. regulation. The U.S.-specific CIP amendment is valid for U.S. sites, even if differing from this CIP.

A deviation is any failure to follow, intentionally or unintentionally, the requirements of the CIP, including laws, guidelines and other regulation as far as required by the CIP, as well as applicable amendments. Deviations that are likely to seriously affect or that actually have seriously affected the rights or safety or wellbeing of subjects or the scientific integrity of the clinical investigation are major deviations (in the U.S. the term "violation" will be used). Otherwise they are minor deviations (in the U.S. simply referred to as "deviations").

Erroneous, spurious or missing data in a CRF is not a deviation in itself and is handled according to the query processes described in the data management section of this CIP. However, the underlying reason might be a deviation.

Intentional, anticipated deviations from the CIP are only allowed if the deviation is required to protect the subject's rights, safety and well-being or the scientific integrity of the study. In such a case, the investigator will contact the sponsor and obtain prior approval for the deviation. If the deviation occurs in an emergency situation or any other unforeseen situation and is required to protect the patient's life or wellbeing, no prior sponsor approval is required. In case of a study deviation, either anticipated or unanticipated, both the investigator as well as the sponsor may request drop-out/premature study termination of the patient, based on the nature and/or consequences of the deviation.

14.2 Recording, reporting and analysing deviations

14.2.1 Site specific deviations

Investigational sites inform the sponsor immediately about any deviation as they become aware of it. In addition, compliance to the CIP is verified by the sponsor through monitoring visits. Each site-specific deviation is recorded by monitors in the respective site deviation log and assessed 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 will be discussed with the PI or authorized designee. A re-training to the respective CIP specification will be performed to prevent further deviations. The retraining will be documented accordingly. Other additional suitable actions may be initiated after consultation of the clinical project management. All information from site deviation logs is consolidated by the sponsor in one overall study deviation log.

14.2.2 Other deviations

Deviations by sponsor personnel or third parties are reported immediately to the sponsor by anyone who becomes aware of it. They are recorded in the study deviation log and assessed for the need of corrective or preventive actions.

14.2.3 Reporting

Deviations are reported in the final clinical investigation report.

14.3 Notification requirements and timelines

The investigator shall notify the sponsor immediately after any major deviation from the CIP which has been proceeded to protect the life or physical well-being of a subject in an emergency situation. All deviations will be documented by the responsible CRA.

The sponsor records specific notification requirements of the involved ECs and CAs and assures that the required timelines are respected.

14.4 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 overall study deviation log 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. Performance and implementation of these actions are documented by the sponsor and filed in the Central File and, in the case of site-specific deviations, in the respective Investigator Site File.

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 patients.

15 DEVICE ACCOUNTABILITY

All medical devices used in this clinical study carry a CE mark and will be used within their intended use. For sites not located in the CE area market approval of the devices is available according to national regulations. Therefore, this investigation does not require a dedicated device accountability procedure.

For sites not located in the CE area the respective national regulations concerning device accountability will be followed as applicable.

16 STATEMENT OF COMPLIANCE

16.1 Applicable ethical standards

The study will be conducted in compliance with the principles that have their origin in the Declaration of Helsinki (current version).

The study will be registered at the publicly accessible database ClinicalTrials.gov.

16.2 Applicable international and national standards

The study will be conducted in compliance with the international standard ISO 14155 "Clinical investigation of medical devices for human subjects – Good clinical practice". For U.S. sites, the clinical investigation will be conducted in compliance with ICH-GCP standards and all applicable FDA regulations and local laws; however, adverse event definitions follow the ISO convention.

For sites located in the CE area in deviation to ISO 14155, no dedicated Investigator's Brochure (IB) is provided. The investigational device is CE marked and used within the intended use, therefore the instruction for use is considered sufficient and substitutes the IB.

The study will also be conducted according to the applicable national legal requirements of the participating investigation sites.

16.3 Ethics committee and competent authority

The study will not begin at an investigation site until favourable opinion of the responsible EC has been obtained for that site and approval of the CA (if applicable) has been granted for the conduct of the study in the respective country.

A copy of the EC/IRB/CA votes will be provided to all principle investigators identifying the documents and amendments on which the opinion was based prior to initiation of the respective investigational site.

16.4 Statement of adherence to additional requirements

If any additional requirements will be imposed by an EC or a CA, these requirements will be followed, if appropriate.

16.5 Statement on subject insurance

All participants of this clinical study are insured against study related injury according to applicable provisions of law. In case of any injuries possible related to the patient's participation in the study, the patient should inform the investigator.

The insurance of the sponsor does not relieve the investigator and the collaborators of any obligation to maintain their own liability policy.

17 INFORMED CONSENT PROCESS

17.1 General considerations

The informed consent procedure is performed by the PI or any investigator designated for this task as recorded in the site responsibility log. The investigator has to fully inform the patient of all pertinent aspects of the clinical investigation in language and terms she/he is able to understand. Any form of coercion, improper influence or inducement of the patient to participate must be avoided. Vulnerable persons (by the investigator's judgment) will be excluded from participation.

If during the course of the clinical investigation new information emerges, the investigator informs the patient accordingly. If this information concerns safety aspects or other aspects that could influence the decision of the patient to continue participating in the study, the patient shall be informed immediately.

The Informed Consent Form (ICF) consists of two parts, the Patient Information and the Informed Consent Signature Form. Both parts must be reviewed and approved by the EC/IRB and CA, if applicable, prior to its use. Any modifications to the Patient Information or Informed Consent Signature Form require prior approval from the EC/IRB/CA and the study sponsor. Samples of the most recently approved versions of these documents will be filed in the Investigator Site File and the Central File at the sponsor.

The patient informed consent process consists of three steps, outlined below.

17.1.1 Informing the patient

The information provided to the patient will include, but is not limited to:

- The risks and benefits associated with participation in this study.
- Treatments alternative to those investigated in this study.
- Privacy provisions and disclosure of personal health information to third parties.
- The voluntary nature of the patient's participation and the right to refuse participation or withdraw from the study at any time without consequences for further treatment.

The study sponsor will prepare an ICF including this information. It is the responsibility of the investigator to ensure that the patient is appropriately informed and that any questions from the patient with respect to his/her participation in this study are adequately answered.

17.1.2 Allowing the patient ample time to decide

After providing the information, the patient should be allowed enough time to consider participation in this study. Any additional questions or concerns that may arise after providing the initial information should be addressed and answered adequately before the patient makes the decision regarding his/her participation.

17.1.3 Documentation of the process

If a patient decides to participate in this study, he/she should sign the Informed Consent Signature Form. This form will be dated and signed by the patient and the investigator. The signed and dated ICF will be filed in the Investigator Site File at the investigational site. Except for monitoring purposes this form will not be disclosed to the study sponsor. Copies of the signed and dated ICF will be provided to the patient and IHF. The conduction of the informed consent process and patient's participation in the BIO|GUARD-MI study should be documented in the hospital's medical records of the patient.

Signing of the ICF is the formal moment of enrollment. No study related procedure or data collection will be performed prior to signature of the ICF by patient and by investigator. Pre-screening of the patient record in respect to the inclusion and exclusion criteria is not a study specific procedure.

17.2 Special circumstances for informed consent

Inclusion of subjects unable to read or write:

Informed consent will be obtained through a supervised oral process if a subject is unable to read or write. An independent witness will be present throughout the process. The written ICF and any other information will be read aloud and explained to the prospective subject and, whenever possible, either will sign and personally date the ICF. The witness also signs and personally dates the ICF attesting that the information was accurately explained and that informed consent was freely given.

18 ADVERSE EVENTS AND DEVICE DEFICIENCIES

In the course of the clinical investigation, undesired medical events can occur in participating patients, which are called AEs in the following. Furthermore, DD may also be observed. All AEs and DDs of the investigational device shall be assessed by the investigator and shall be documented and reported throughout the clinical investigation within the timelines defined below. For the U.S. sites adverse event reporting is required according to 21 CFR 812. However, due to the requirements of the sponsor located in Europe, U.S sites will also have to follow reporting according to ISO 14155 standards. Detailed reporting requirements for U.S. sites within the U.S are defined in the U.S.-specific amendment of the BIO|GUARD-MI study.

The investigator shall document all events on the respective CRF pages provided within the EDC system. The indicated timelines for reporting of initial cases and possible update reports shall be strictly followed (see Table 4: Reporting responsibilities of the investigator).

According to ISO 14155 events will be classified on the basis of the definitions below.

18.1 Definition of adverse events

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 investigational 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 investigational medical devices.

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

- Pre-existing 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 patient 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.

18.2 Definition of adverse device effects

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. anaesthetic complications, wound healing disturbances etc) are considered as procedure related ADEs.

18.2.1 Causality assessment

The relationship between the use of the investigational device (including the medical-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. As defined in the Meddev 2.7/3 rev 3, 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 investigational 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 investigational device seems relevant and/or the event cannot be reasonably explained by another cause, but additional information may be obtained.

Causal relationship: the serious event is associated with the investigational device or with procedures beyond reasonable doubt.

The investigators will distinguish between the serious 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 investigational device in response to an adverse event (the BioMonitor is replaced), the replacement will be considered like an initial application of a new investigational device and shall be assessed accordingly.
- Replacement of the BioMonitor due to a regular battery depletion is not considered an adverse event.
- An adverse event can be related both to procedures and the investigational device. Complications of procedures are considered not related if the said procedures would

have been applied to the patients also in the absence of investigational device use or application.

18.3 Definition of 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 form. In case the DD did not cause an adverse event, the provided DD form shall be used to document this "non-medical" event.

If a 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 is classified as a DD with SADE potential.

18.4 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 foetal distress, fatal death or a congenital abnormality or birth defect.

Note: Hospitalizations planned before enrollment for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered as serious adverse event.

In-patient hospitalization is defined as at least one overnight stay (change of date) in a hospital. In case, a patient is only for some hours in the hospital (without change of date) this event 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 CA and 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 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.

Note: In order to comply with the German national legislation, the German sites shall report to the sponsor all events which resulted or could have resulted in the consequences of a serious adverse event as serious adverse event (see also section 18.8).

18.5 Definition of serious adverse device effect

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

18.6 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 version of the risk analysis report.

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 risk analysis report.

18.7 Anticipated adverse events

See section 6.2.

18.8 Reporting responsibilities

In addition to reporting responsibilities defined below, for sites located in the U.S. also U.S. specific reporting requirements need to be fulfilled. Details on these national requirements are documented in the U.S. specific amendment to the BIO|GUARD-MI CIP.

18.8.1 Reporting responsibilities of the investigator to sponsor

The investigator shall document all events on the respective eCRF pages provided within the EDC system. The indicated timelines for reporting of initial cases and possible update reports shall be strictly followed.

All adverse events (AE) and adverse device effects (ADEs) shall be reported together with an assessment by completing the AE-CRF in accordance with ISO 14155. Note: For German sites, the (S)A(D)E definition according to the German national regulation MPSV[8] §2 (5)[9] should be applied.

[8] Medizinprodukte-Sicherheitsplanverordnung vom 24.Juni 2002 (BGBl. I S.2131) zuletzt geändert durch Artikel 3 der Verordnung über klinische Prüfungen von Medizinprodukten und zur Änderung medizinprodukterechtlicher Vorschriften vom 10.Mai 2010 (BGBl. I. S. 560)

[9] Im Sinne der MPSV ist ein schwerwiegendes unerwünschtes Ereignis jedes in einer genehmigungspflichtigen klinischen Prüfung oder einer genehmigungspflichtigen Leistungsbewertungsprüfung auftretende ungewollte Ereignis, das unmittelbar oder mittelbar zum Tod oder zu einer schwerwiegenden Verschlechterung des Gesundheitszustands eines Probanden, eines Anwenders oder einer anderen Person geführt hat, geführt haben

For device deficiencies of the investigational device, a DD-CRF shall be completed.

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 patient 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 diagnose 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 patient 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.

18.8.2 Reporting responsibilities of the investigator to other parties

According to national and international regulations some of the involved CAs and ECs request reporting of SAEs and DDs with SADE potential during the course of the study. Investigators have to ensure, that they fulfil the reporting obligations of their local CAs and EC/IRBs.

Table 4: Reporting responsibilities of the investigator

Event	Report to	Timeline
Adverse Event (AE) / Adverse Device Effect (ADE)	CCR BIOTRONIK SE & Co. KG: • *Documentation in (S)A(D)E-CRF in iMedNet*	Within 2 weeks
Serious Adverse Event (SAE) / Serious Adverse Device Effect (SADE)	CCR BIOTRONIK SE & Co. KG: • *Documentation in (S)A(D)E -CRF in iMedNet*	1) Immediately, latest 24h after detection
Unanticipated Serious Adverse Device Effect (USADE)	CCR BIOTRONIK SE & Co. KG: • *Documentation in (S)A(D)E -CRF in iMedNet*	1) Immediately, latest 24h after detection
Device Deficiencies	CCR BIOTRONIK SE & Co. KG: • *Documentation in the DD-CRF in iMedNet*	Within 14 days
Device Deficiency with SADE potential	CCR BIOTRONIK SE & Co. KG: • *Documentation in DD-CRF in iMedNet*	1) Within 24 hours

könnte oder führen könnte ohne zu berücksichtigen, ob das Ereignis vom Medizinprodukt verursacht wurde; das Vorgesagte gilt entsprechend für schwerwiegende unerwünschte Ereignisse, die in einer klinischen Prüfung oder Leistungsbewertungsprüfung, für die eine Befreiung von der Genehmigungspflicht nach § 20 Absatz 1 Satz 2 des Medizinproduktegesetzes erteilt wurde, aufgetreten sind.

18.8.3 Reporting responsibilities of the sponsor

BIOTRONIK SE & Co. KG will report all SAEs/SADE and all Device Deficiencies with SADE potential to the CAs and ECs depending on the local regulatory requirements.

For the CAs and ECs or IRBs located in the U.S., the local sponsor will report all concerned events according to the national requirements. Details on these national requirements are documented in the U.S. specific amendment to the BIO|GUARD-MI CIP.

Furthermore, BIOTRONIK SE & Co. KG ensures that summarized Safety Reports are forwarded to the investigational sites and the ethic committees depending on the local requirements.

For the investigational sites and ethics committees or IRBs located in the U.S., the local sponsor will forward all concerned reports according to the national requirements. Details on these national requirements are documented in the U.S. specific amendment to the BIO|GUARD-MI CIP.

BIOTRONIK SE & Co. KG will inform the investigators about all reported SAEs and DDs that could have led to a SADE on a regular basis. Event listings will be provided regularly and unanticipated serious adverse device effects (USADEs) will be reported immediately.

For investigators located in the U.S., the local sponsor will report all concerned events and listings according to the national requirements. Details on these national requirements are documented in the U.S. specific amendment to the BIO|GUARD-MI CIP.

18.9 Reporting timelines

Reporting timelines for investigators are stated in the corresponding Table 4 in section 18.8.

18.10 Emergency contact

A contact address for patients in case of emergency will be provided in the individual ICFs.

In case technical support is needed the service hotline of BIOTRONIK is available 24 hours a day. Phone: +49 (0) 30 68905-1133. For technical support for other devices used in the study, please consult the respective manual or support team.

19 VULNERABLE POPULATION

Enrollment of patients from a vulnerable population is not anticipated for this study. The PI has to take decision about the vulnerability of patients and where appropriate ensure that these patients are not enrolled. Examples for vulnerability are an age below 18 years, limited contractual capability, and dependence from sponsor or site.

20 SUSPENSION

20.1 Criteria and procedures

The study may be suspended or terminated prematurely in all sites or in a single investigational site based on a decision by the sponsor, the investigator or the EC/IRB/CA. A consultation of all parties involved prior to study termination is preferable. Reasons for premature study termination should be documented in an adequate way.

The sponsor has the right for premature study termination of the whole study, of single study phases or groups, or to exclude single investigational sites from further study participation.

Reasons for termination may be:

- Occurrence of severe adverse events that result in a non-acceptable risk for further study participation
- The number of premature study terminations exceeds the tolerable percentage of drop-outs so that proper completion of the study cannot be expected anymore
- Insufficient enrollment rates so that proper completion of the study cannot be expected anymore (see section 20.1.1 with regard to the exclusion of single investigational sites)
- Results from other clinical trials indicate a non-tolerable risk for further conduction of this study
- Attempted fraud or fraud that may be evidenced
- Poor data quality
- Missing compliance of the respective investigator or study site (e.g. persistent incompliance with the CIP or regulatory requirements)

In case the study sponsor decides to suspend or prematurely terminate the study, the sponsor is required to promptly notify the investigator(s) to whom the decision applies. The investigator will inform the EC/IRB/CA of this decision. The investigator will also promptly inform all patients enrolled at the investigational site and are still actively participating. Patients that already left the study shall be informed if they might be affected by safety aspects.

In case of any reasonable ethical concern of the investigator regarding a further study conduct in the respective investigational site, the sponsor shall be informed immediately. If the investigator decides to suspend or prematurely terminate the study at his/her site he/she will promptly inform the study sponsor, the EC/IRB/CA and all enrolled patients of this decision.

If the EC/IRB/CA decides to suspend or prematurely terminate the study, the investigator will promptly inform the study sponsor (or vice versa as applicable) and all enrolled patients of this decision.

The eCRF for "Study Termination" has to be completed in all of the above cases.

All open eCRFs have to be completed as far as possible by the investigational site.

20.1.1 Replacement strategy

Each participating study site is obligated to meet the estimated enrollment rate as determined during the qualification visit. However, every investigator can enroll as many patients as desired until the sample size has been reached and announced.

The enrollment rate of each site will be evaluated by the study team on a monthly basis. The site will be informed immediately in case it is foreseeable that the enrollment expectations are not met. In parallel the study team and respective field CRA will offer to provide additional support to prevent a possible replacement. However, if despite all efforts taken no patient could be enrolled after 3 months the respective site will be closed and replaced.

20.2 Un-blinding procedures

Un-blinding procedures are not applicable since the study design is open.

20.3 Requirements for subject follow-up

In case of a study suspension no new patients will be enrolled until the suspension has been lifted. During the suspension, follow-up and data collection will continue as per CIP. If the suspension is due to an EC/IRB/CA decision, additional requirements from the EC/IRB/CA with respect to follow-up and data collection may apply.

Ongoing SADEs will be followed in a time period of up to 6 weeks after pre-mature or regular study termination of the individual patient in order to follow the outcome, clarify open questions or for collection of missing information concerning the respective SADE.

Patients will be informed on this procedure in written form in the ICF.

21 PUBLICATION POLICY

21.1 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.

21.2 Authorship guidelines

21.2.1 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.

21.2.2 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 fulfil 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.

21.2.3 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 weight 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.

21.2.4 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 four components:

- ➔ **Enrollment** of patients,
- ➔ prompt **classification of arrhythmias** detected by the ICM,
- ➔ unhesitating **contact to the patient** and
- ➔ conducting an **in-office termination visit**.

Justification:

The importance of enrollments for the study's success is evident. Without prompt classification of arrhythmias and the consecutive contact of patients, the study concept cannot be effective. The conduction of in-office termination visits is important for a complete adverse event reporting.

All four elements can be objectively calculated from the study database and together, they provide an objective quantification of the contribution of a study site.

21.2.5 Calculation of the total score

For each of the four elements, 1000 points are granted.

- ➔ For each randomized patient, the number of granted points to the investigational site is 1000 divided by the number of randomized patients.
- ➔ Further 1000 points are distributed evenly over all classified arrhythmias, which have been completed within 5 working days after onset of the arrhythmia.
- ➔ Equally, further 1000 points are distributed evenly over all documented contacts to patients after arrhythmias, which were done within 7 working days of the arrhythmia.
- ➔ For each patient seen in-office for the final study termination visit, the number of points is 1000 divided by the total number of patients seen in-office for the final study termination visit.

The sites will then be ranked by the total sum of points from the four categories.

For all publications after the primary publication, investigators who have not been authors of accepted publications will be considered preferentially. The number of authors of a study site on all publications (weighted by the journals' latest impact factors) shall be proportional to the data contribution measured by the score, which is described here.

21.2.6 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

21.2.7 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, favour investigators who have contributed more data to the specific subject of the publication.

21.2.8 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.

21.2.9 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.

21.2.10 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.

21.2.11 Reimbursement

No honoraria will be paid for authorship of publications.

22 BIBLIOGRAPHY

(1) Steg PG, James SK, Atar D et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2012;33:2569-2619.

(2) World Health Organization (WHO). Fact Sheet: The top 10 causes of death. 1-5-2014. World Health Organization (WHO). Ref Type: Internet Communication

(3) Chan MY, Sun JL, Newby LK et al. Long-term mortality of patients undergoing cardiac catheterization for ST-elevation and non-ST-elevation myocardial infarction. *Circulation* 2009;119:3110-3117.

(4) Garcia-Garcia C, Subirana I, Sala J et al. Long-term prognosis of first myocardial infarction according to the electrocardiographic pattern (ST elevation myocardial infarction, non-ST elevation myocardial infarction and non-classified myocardial infarction) and revascularization procedures. *Am J Cardiol* 2011;108:1061-1067.

(5) Polonski L, Gasior M, Gierlotka M et al. A comparison of ST elevation versus non-ST elevation myocardial infarction outcomes in a large registry database: are non-ST myocardial infarctions associated with worse long-term prognoses? *Int J Cardiol* 2011;152:70-77.

(6) van Leeuwen MA, Daemen J, van Mieghem NM et al. Comparison of long-term outcomes in STEMI and NSTE-ACS after coronary stent placement: an analysis in a real world BMS and DES population. *Int J Cardiol* 2013;167:2082-2087.

(7) Camm AJ, Kirchhof P, Lip GY et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J* 2010;31:2369-2429.

(8) Hohnloser SH, Kuck KH, Dorian P et al. Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. *N Engl J Med* 2004;351:2481-2488.

(9) Huikuri HV, Castellanos A, Myerburg RJ. Sudden death due to cardiac arrhythmias. *N Engl J Med* 2001;345:1473-1482.

(10) Solomon SD, Zelenkofske S, McMurray JJ et al. Sudden death in patients with myocardial infarction and left ventricular dysfunction, heart failure, or both. *N Engl J Med* 2005;352:2581-2588.

(11) Jons C, Thomsen PE. Treating cardiac arrhythmias detected with an implantable cardiac monitor in patients after an acute myocardial infarction. *Curr Treat Options Cardiovasc Med* 2012;14:39-49.

(12) Bloch Thomsen PE, Jons C, Raatikainen MJ et al. Long-term recording of cardiac arrhythmias with an implantable cardiac monitor in patients with reduced ejection fraction after acute myocardial infarction: the Cardiac Arrhythmias and Risk Stratification After Acute Myocardial Infarction (CARISMA) study. *Circulation* 2010;122:1258-1264.

(13) Furukawa T, Maggi R, Bertolone C et al. Effectiveness of remote monitoring in the management of syncope and palpitations. *Europace* 2011;13:431-437.

(14) Antoni ML, Hoogslag GE, Boden H et al. Cardiovascular mortality and heart failure risk score for patients after ST-segment elevation acute myocardial infarction treated with primary percutaneous coronary intervention (Data from the Leiden MISSION! Infarct Registry). *Am J Cardiol* 2012;109:187-194.

(15) Marchioli R, Avanzini F, Barzi F et al. Assessment of absolute risk of death after myocardial infarction by use of multiple-risk-factor assessment equations: GISSI-Prevenzione mortality risk chart. *Eur Heart J* 2001;22:2085-2103.

(16) Ruwald AC, Gang U, Thomsen PE et al. The predictive value of CHADS(2) risk score in post myocardial infarction arrhythmias - a Cardiac Arrhythmias and RIsk Stratification after Myocardial infArction (CARISMA) substudy. *Int J Cardiol* 2014;173:441-446.

(17) Chao TF, Liu CJ, Chen SJ et al. CHADS2 score and risk of new-onset atrial fibrillation: a nationwide cohort study in Taiwan. *Int J Cardiol* 2013;168:1360-1363.

(18) Chua SK, Shyu KG, Lu MJ et al. Clinical utility of CHADS2 and CHA2DS2-VASc scoring systems for predicting postoperative atrial fibrillation after cardiac surgery. *J Thorac Cardiovasc Surg* 2013;146:919-926.

(19) Suzuki S, Sagara K, Otsuka T et al. Usefulness of frequent supraventricular extrasystoles and a high CHADS2 score to predict first-time appearance of atrial fibrillation. *Am J Cardiol* 2013;111:1602-1607.

(20) Barrett TW, Abraham RL, Jenkins CA, Russ S, Storrow AB, Darbar D. Risk factors for bradycardia requiring pacemaker implantation in patients with atrial fibrillation. *Am J Cardiol* 2012;110:1315-1321.

(21) Gang UJ, Jons C, Jorgensen RM et al. Clinical significance of late high-degree atrioventricular block in patients with left ventricular dysfunction after an acute myocardial infarction--a Cardiac Arrhythmias and Risk Stratification After Acute Myocardial Infarction (CARISMA) substudy. *Am Heart J* 2011;162:542-547.

(22) Vardas PE, Auricchio A, Blanc JJ et al. Guidelines for cardiac pacing and cardiac resynchronization therapy: The Task Force for Cardiac Pacing and Cardiac Resynchronization Therapy of the European Society of Cardiology. Developed in collaboration with the European Heart Rhythm Association. *Eur Heart J* 2007;28:2256-2295.

(23) Ahmed I, Nelson WB, House CM, Zhu DW. Predictors of appropriate therapy in patients with implantable cardioverter-defibrillator for primary prevention of sudden cardiac death. *Heart Int* 2010;5:e4.

(24) Al-Khatib SM, Granger CB, Huang Y et al. Sustained ventricular arrhythmias among patients with acute coronary syndromes with no ST-segment elevation: incidence, predictors, and outcomes. *Circulation* 2002;106:309-312.

(25) Desai H, Aronow WS, Tsai FS et al. Statins reduce appropriate cardioverter-defibrillator shocks and mortality in patients with heart failure and combined cardiac resynchronization and implantable cardioverter-defibrillator therapy. *J Cardiovasc Pharmacol Ther* 2009;14:176-179.

(26) Kallmunzer B, Breuer L, Kahl N et al. Serious cardiac arrhythmias after stroke: incidence, time course, and predictors--a systematic, prospective analysis. *Stroke* 2012;43:2892-2897.

(27) Montalescot G, Sechtem U, Achenbach S et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J* 2013;34:2949-3003.

(28) Zipes DP, Camm AJ, Borggrefe M et al. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death) developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Europace* 2006;8:746-837.

(29) Hermann G. Master Study of the Implantable Cardiac Monitor BioMonitor, Interim Report. 12-5-2014.
Ref Type: Generic

(30) Moss AJ, Zareba W, Hall WJ et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002;346:877-883.

(31) Braunwald E, Domanski MJ, Fowler SE et al. Angiotensin-converting-enzyme inhibition in stable coronary artery disease. *N Engl J Med* 2004;351:2058-2068.

(32) Fox KM. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet* 2003;362:782-788.

(33) Kruk M, Buller CE, Tcheng JE et al. Impact of left ventricular ejection fraction on clinical outcomes over five years after infarct-related coronary artery recanalization (from the Occluded Artery Trial [OAT]). *Am J Cardiol* 2010;105:10-16.

(34) Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 2000;342:145-153.

(35) Krahn AD, Klein GJ, Yee R, Takle-Newhouse T, Norris C. Use of an extended monitoring strategy in patients with problematic syncope. Reveal Investigators. *Circulation* 1999;99:406-410.

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

(37) Seidl K, Rameken M, Breunung S et al. Diagnostic assessment of recurrent unexplained syncope with a new subcutaneously implantable loop recorder. Reveal-Investigators. *Europace* 2000;2:256-262.

(38) Sanna T, Diener HC, Passman RS et al. Cryptogenic stroke and underlying atrial fibrillation. *N Engl J Med* 2014;370:2478-2486.

(39) Smit J, Korup E, Schonheyder HC. Infections associated with permanent pacemakers and implanted cardioverter-defibrillator devices. A 10-year regional study in Denmark. *Scand J Infect Dis* 2010;42:658-664.

(40) Tarakji KG, Chan EJ, Cantillon DJ et al. Cardiac implantable electronic device infections: presentation, management, and patient outcomes. *Heart Rhythm* 2010;7:1043-1047.

(41) Brignole M, Vardas P, Hoffman E et al. Indications for the use of diagnostic implantable and external ECG loop recorders. *Europace* 2009;11:671-687.

(42) Varma N, Epstein AE, Irimpen A, Schweikert R, Love C. Efficacy and safety of automatic remote monitoring for implantable cardioverter-defibrillator follow-up: the Lumos-T Safely Reduces Routine Office Device Follow-up (TRUST) trial. *Circulation* 2010;122:325-332.

(43) Wassmer G. Planning and Analyzing Adaptive Group Sequential Survival Trials. Biometrical Journal 2006; 48: 714–29 statt Lehmacher W, Wassmer G. Adaptive sample size calculations in group sequential trials. Biometrics 1999;55:1286-1290.

(44) Schoenfeld DA. Sample-size formula for the proportional-hazards regression model. *Biometrics* 1983;39:499-503.

(45) Pocock SJ, Geller NL, Tsiatis AA. The analysis of multiple endpoints in clinical trials. *Biometrics*1987;43:487-498.

23 APPENDICES

23.1 Appendix A: Comparison BIO|GUARD-MI CIP with U.S.-specific CIP amendments

To meet the regulatory requirements for U.S. investigational sites when conducting an IDE study, the CIP V7.0 of the BIO|GUARD-MI study is transferred into an amendment, dated April 06, 2021 to the U.S.-specific protocol version June 12, 2019. This appendix list compares the U.S. specific protocol to the current CIP version 7.0 valid for all out-of-U.S. investigational sites. All critical aspects of the study including design and objectives, primary endpoints, secondary endpoints, additional data of interest, enrollment/implant/follow-up procedures, inclusion criteria, exclusion criteria, adverse event reporting and Board processes, are identical. The similarity in the clinical study design justifies the planned pooling of data from subjects enrolled under both protocols (U.S. and non-U.S.) to meet the sample size requirements for the analysis of the primary endpoints.

An obvious difference between the two protocol versions is the order of sections and formatting. However, the content is only changed according to the documentation below.

The table below outlines the similarities and differences between the protocols.

Title	**BIOGUARD MI, version 7.0**	**BIOGUARD MI, U.S. version June 12, 2019 amended April 06, 2021**	**Justification**
General Aspects			
Clinical Trials Registration	NCT02341534		Single posting
Region	Outside U.S.	U.S.	All data will be collected with the same EDC system. Therefore, all data collection is identical
Clinical sites	~ 60 sites outside U.S.	~ 20 U.S. sites	Up to 80 sites total
Number of subjects	Up to 2900 worldwide	Up to 360 in the United States (total worldwide 2900)	FDA submission requires a total number of subjects from US sites. Overall, the study will include up to 2900 subjects, which includes the 360 from the United States
Sample size	The original planning assumed that 372 primary events would be required to accept the primary alternative hypothesis with 80% statistical power given an assumed hazard ratio in the population of 0.7452, and the study was to be terminated after this number of endpoints had been collected. Instead, it was decided to enter the termination phase without any avoidable further delay. Therefore, the intended number of endpoints may not be reached.		Identical sample size calculation

Title	BIOGUARD MI, version 7.0	BIOGUARD MI, U.S. version June 12, 2019 amended April 06, 2021	Justification
Coordinating Clinical Investigator	[redacted]		Identical Coordinating Clinical Investigator
Sponsor	BIOTRONIK SE & Co. KG Woermannkehre 1 12359 Berlin Germany	BIOTRONIK, Inc. 6024 Jean Road Lake Oswego, OR 97035 USA	BIOTRONIK SE & Co. KG recognized as the global sponsor, while BIOTRONIK, Inc. is the local sponsor for all U.S. sites
Boards and Committees	Central Electrocardiogram Monitoring Board (CEMB) Data Safety Monitoring Board (DSMB) Endpoint and Adverse Event Committee (EAEC) Steering Committee (SC) Publication Steering Committee (PSC)		Identical boards and committees
Contract Research Organization	IHF GmbH Institut für Herzinfarktforschung Bremserstraße 79 67063 LudwigshafenGermany		In the course of the study, additional service providers might be contracted depending on the countries which will be further included.
Applicable regulation	ISO 14155 and national country-specific regulations	ICH/GCP according to FDA requirements (21 CFR Part 812)	Study procedures in the U.S. follow FDA requirements. However, additional requirements of ISO14155 may be applicable in specific tasks (e.g. AE reporting)
Clinical Report Requirements	Clinical reports will follow reporting requirements per ISO14155	Clinical reports will follow FDA reporting requirements for IDE studies. This includes an annual progress report and a current list of investigators every 6 months, in addition to the final report.	Clinical reports will follow the requirements in the associated region.
Noncompliance with study protocol	Noncompliance classification: Major Deviation: Deviation that are likely to seriously affect or that actually have seriously affected the rights or safety of wellbeing of subjects or the scientific integrity of the clinical investigation. Minor deviation: Other deviation from the protocol that do not meet the definition for Major Deviation. All protocol noncompliances are recorded by each site on a paper deviation log	Noncompliance classification: Protocol Violation: Major deviation where the protocol requirements and/or regulatory guidelines are not followed, and are generally more serious in nature. They are considered to potentially affect the scientific soundness of the study and/or rights, safety or welfare of subjects. Protocol Deviation: Other deviation from protocol that does not meet the definition of violation and 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. All protocol noncompliances are recorded on a Protocol Non-compliance eCRF within the EDC system.	Noncompliance classifications in the regions are similar in definition, but each protocol follows the applicable regulatory requirements. The statements vary in sentence structure and word choice. The U.S. records noncompliances electronically as part of their standard processes. All noncompliances from both regions will be merged for reporting purposes.

Title	BIOGUARD MI, version 7.0	BIOGUARD MI, U.S. version June 12, 2019 amended April 06, 2021	Justification
SAE/S(U)ADE/DD	Per ISO14155 The investigator reports: • Adverse events • Serious adverse events • Serious adverse device effect • Unanticipated serious adverse device effect • Device deficiency	Per ISO 14155 and FDA 21 CFR Part 812 The investigator reports: • Adverse events • Serious adverse events • Unanticipated adverse device effects • Serious adverse device effect • Unanticipated serious adverse device effect • Device deficiency • Device complaint	To ensure proper reporting, all sites will follow ISO14155 and U.S. sites will follow FDA 21 CFR Part 812, in addition to ISO 14155
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 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.		Identical termination criteria
Study Design Aspects			
Design	Prospective, controlled, randomized (1:1), parallel-group, open, multi-center, international study with an event-driven design		Identical study design
Study phases	Study designed in two enrollment phases, 1 and 2 with longer study duration	Due to the timing of the study, the U.S. will only join Phase 2	Information on different phases is reduced in the U.S. protocol, as it is not applicable in this country
Primary objective	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 MI, CHA_2DS_2-VASc Score ≥ 4 in men/ ≥ 5 in women and LVEF > 35%		Identical primary objective
Secondary objective	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.		Identical secondary objective
Primary endpoints	Time to first MACE 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		Identical primary endpoint

Title	BIOGUARD MI, version 7.0	BIOGUARD MI, U.S. version June 12, 2019 amended April 06, 2021	Justification

Secondary endpoints	1. To assess the time to
	• 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
	2. 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
	3. To assess the quality of life WHO (Five) Well-Being Index
			Identical secondary endpoints

Additional data of interest	To assess in a descriptive manner, the types and number of therapeutic interventions administered after arrhythmias detected by remote monitoring		Identical additional data of interest
Inclusion criteria	• Patient has a history of MI according to guidelines • CHA_2DS_2-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		Identical inclusion criteria
Exclusion criteria	• Platelet count < 90.000 per mm^3 or 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		Identical exclusion criteria

Title	BIOGUARD MI, version 7.0	BIOGUARD MI, U.S. version June 12, 2019 amended April 06, 2021	Justification
Exclusion criteria clarification of "non-interventional clinical investigation"	Following the definition of the European clinical trial directive 2001/20/EC, 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.	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.	Similar statement, but the U.S. sites are not bound by the European clinical trial directive 2001/20/EC
Follow-up procedures	**Patient Enrollment** Inclusion and exclusion criteria met Informed consent obtained Enrollment data collected ↓ **Baseline** ↓ **Randomization** Randomization selection included in Baseline eCRF 1:1 randomization to receive BioMonitor Device or standard of care (no BioMonitor device) ↓ **Implantation** Only for subjects randomized to receive a BioMonitor device No later than 8 weeks following Enrollment ↓ **Discharge** Discharge refers to when subjects leave the investigational site where enrollment occurred ↓ **Follow up phone contact (every 6 months)** WHO Quality of Life Questionnaire AE collection ↓ **Termination** End of subject participation Official point of explantation of BioMonitor not mandated by study protocol		Identical study procedures with one exception: the U.S. protocol amendment describes that study personnel will conduct the interview on adverse events at the final study termination visit while CIP version 7.0 specifically identifies the investigator as performing the interview.

Title	BIOGUARD MI, version 7.0	BIOGUARD MI, U.S. version June 12, 2019 amended April 06, 2021	Justification
Discharge	The patient will be further advised to contact the investigational site provided that the general practitioner or cardiologist finds a condition for which it appears that the attention of a tertiary care facility is required. Hence, the patients will be discouraged from contacting the investigational site on his or her own decision, but should only visit the investigational site after being advised to do so.	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.	Each protocol includes discharge instructions that are amenable to regional medical practices
Telephone contact	An external Clinical Research Organization (CRO) will contact all study subjects via phone every 6 months. These calls include questions about subject's health and adverse event assessment, along with the administration of the WHO Quality of Life questionnaire		Identical telephone contact procedures with study subjects
Medical record collection resulting from AEs reported during telephone contact	Telephone follow-up activities and consequent source data collection will be performed by an external CRO contracted by the main sponsor. If the event is an SAE, source data is provided by the CRO.	Telephone follow-up activities and consequent source data tracking will be performed by an external CRO contracted by the main sponsor. The site should try to obtain as much information regarding the adverse event as possible, including all applicable medical records of the event.	Each protocol includes instructions on medical record collection methods that are amenable to regional medical practices
Investigational Medical Devices			
Investigational Medical Devices	BioMonitor or approved successor		Identical medical devices currently, but future successors may not be utilized at same time due to varying CE/FDA approval dates
Accessory components to investigational medical devices	BIOTRONIK Home Monitoring®: CardioMessenger II, IIs or successors, programmer: Renamic, ICS 3000 or successors with current software version, accessory device Remote Assistant if applicable		Identical accessory components currently, but future successors may not be utilized at the same time due to varying CE/FDA approval dates

Title	BIOGUARD MI, version 7.0	BIOGUARD MI, U.S. version June 12, 2019 amended April 06, 2021	Justification
Indications for use	The BioMonitor is an ICM used to automatically detect and record episodes of arrhythmia in patients at risk for bradycardia, tachycardia, asystole and AF. The ICM is not intended to deliver any therapy. The device reports the recorded episodes and the related statistical data via a physician's programmer and telemetrically via BIOTRONIK Home Monitoring®.	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	Intended use is similar. The U.S. protocol includes the indications for use verbatim from the FDA clearance of the BioMonitor 2 (Form 3881).
Contraindications	There are no known contraindications		Contraindications, or current lack thereof, are identical
Miscellaneous			
Responsibilities of investigator	Within protocol	Removed from protocol	The U.S. uses Investigator agreements (PI agreements and sub-investigator agreements). These ancillary documents include all investigator responsibilities.
Monitoring	Within protocol	Brief review of monitoring methods, monitors and monitoring visits included. Noted that more detail is included within the Monitoring Plan, separate from the protocol	The U.S. protocol references the Monitoring Plan, as this is a detailed document that is best suited for the IDE application requirement of providing monitoring procedures
Informed Consent process	Detailed explanation of informed consent process in the protocol according to ISO14155 European data protection regulation.	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.	Informed Consent processes are largely similar in definition, but each protocol follows the applicable regulatory requirements.

Title	BIOGUARD MI, version 7.0	BIOGUARD MI, U.S. version June 12, 2019 amended April 06, 2021	Justification
Data retention and archiving	All study related electronic documents are stored in the archive of BIOTRONIK which provides storage conditions free from risk of fire, flood, theft and vermin. The access to the files is controlled. After CDMS closure, all eCRF data, the audit trail and other relevant CDMS content are exported and stored electronically for at least 15 years on the archive server.	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. Furthermore BIOTRONIK Inc will provide copies of the data for U.S. subjects to BIOTRONIK SE & Co. KG. 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.	Implementation of logistical aspects in the U.S. protocol assure adequate archiving of data.
Record storage requirement for investigational sites	The sites have to ensure data availability during the whole archiving period, i.e. for 15 years.	Record storage requirements will be consistent with local regulatory regulations.	U.S. sites follow 21 CFR 812.140
Confidentiality of Subject Data	All involved parties are bound to data secrecy according to the European Data Protection Regulation (GDPR). All subjects will be informed on all relevant regulations concerning data secrecy and data protection which are applicable for BIO|GUARD-MI in the ICF.		Identical responsibilities of confidentiality of subject data, as both regions are following GDPR.