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Clinical Investigation Plan

for the

BIO|MASTER.BIOMONITOR III

Reference Number:	BA109
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Investigational device:	BIOMONITOR III

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List of principal investigators, investigation(al) sites, and institutions

A current list of the principal investigators at each investigational site, the address details for each investigational site, the emergency contact details for the principal investigator at each site 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 have read this Clinical Investigation Plan (CIP) and agree to adhere to the requirements described in this study protocol.

I will provide copies of this study protocol and all necessary information about this study to the staff under my supervision.

I will discuss this material with them and ensure they are fully informed about the devices under investigation as well as all aspects concerning the conduct of this study.

_____ _____

City, date Signature of Principal Investigator

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1 LIST OF ABBREVIATIONS

ADE	Adverse Device Effect
AE	Adverse Event
AF	Atrial Fibrillation
AIMD	Active Implantable Medical Device (Directive 90/385/EEC)
ASADE	Anticipated Serious Adverse Device Effect
AU	Australia
bpm	Beats Per Minute
CA	Competent Authority
CCR	Center for Clinical Research; BIOTRONIK SE & CO. KG study department
CDMS	Clinical Datamanagement System
CE	CE mark, a stylized "CE" (Conformité Européenne) placed on products to signify conformance with European Union regulations
CEC	Clinical Event Committee
CFR	Code of Federal Regulations der USA (www.gpoaccess.gov/cfr)
CI	Coordinating Investigator
CIP	Clinical Investigation Plan
CIR	Clinical Investigation Report
CRA	Clinical Research Associate
CRF	Case Report Form
CRT	Cardiac Resynchronization Therapy
DAL	Device Accountability Log
DD	Device Deficiency
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EMI	Electromagnetic Interference
EP	Electrophysiology
ESC	European Society of Cardiology
EU	European Union
FDA	US Food and Drug Administration (www.fda.gov)
FIT	Fast Insertion Tool
FPI	First Patient In
FU	Follow-up visit
GDPR	General Data Protection Regulation
HIPAA	Health Insurance Portability and Accountability Act
HM	Home Monitorig

HMSC	Home Monitorig Service Center
HVR	High ventricular rate
Hz	Hertz
ICD	Implantable Cardioverter Defibrillator
ICF	Informed Consent Form
ICH	International Conference on Harmonisation 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
IFU	Instructions For Use (user manual)
iMedNet	Web-based electronic data entry (EDC) system for clinical trials provided by MedNet Solutions Inc.
IIRB	Institutional Review Board
ISO14155	International Organization for Standardization, norm no. 14155
LOC	Loss of conciousness
LPI	Last Patient In
LPO	Last Patient Out
MEDDEV	Collection of guidelines of the European Commission for conformity assessment of medical devices
MedNet	Supplier of Clinical Trial Software (MedNet Solutions, Inc. www.mednetstudy.com)
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging
PAC	Premature Atrial Contraction
PDF	Portable Document Format (www.adobe.com)
PI	Principal Investigator
PMCF	Post Market Clinical Follow-up
PPV	Positive predictive value
PVC	Premature ventricular contraction
QRS	Electrical complex on an ECG related to the depolarization of the ventricles
SaaS	Software as a Service
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistics and Analysis Software produced by SAS Institute Inc. (www.sas.com)
SDS	Source Data Sheet
sECG	subcutaneous echocardiogram
SOP	Standard Operating Procedure
SRD	Sudden rate drop

TGA	Therapeutic Goods Administration
UBD	Used before date
UMTS	Universal Mobile Telecommunications System
US	United States
USA	United States of America
USADE	Unanticipated Serious Adverse Device Effect
USB	Universal Serial Bus
VER	Validation / Verification Results
VES	Ventricular Extrasystole
Vs	Ventricular Sensing Events
ZIP	File compression format

2 SYNOPSIS

Title	BIO|MASTER.BIOMONITOR III
Patient population	The patient population consists of patients in whom long-term cardiac rhythm monitoring is required for diagnostic purposes.
Design	Multicenter, international, prospective, non-randomized, non-controlled, open-label
Investigational device(s)	BIOMONITOR III insertable cardiac monitor, including incision and insertion tool (FIT OneStep)
Objectives	This study is a post-market clinical follow-up (PMCF) study to identify and evaluate residual risks associated with the use of the BIOMONITOR III that are discovered or remain even after risk analysis, risk mitigation and successful conformity assessment. Furthermore, this study will also provide additional data as required by regulatory authorities outside of the CE-region.
Primary endpoint	SADE-free rate related to BIOMONITOR III including incision and insertion tool set until 3-month follow-up
Secondary endpoint(s)	• R-wave amplitude at 1st follow-up and 3-month follow-up • Noise burden at 1st follow-up and 3-month follow-up • P-wave visibility at 1st follow-up and 3-month and 12-month follow-up • SADE-free rate related to BIOMONITOR III from insertion until 12-month follow-up
Inclusion criteria	• Patient is at high risk of developing a clinically important cardiac arrhythmia; **or** Patient is undergoing investigation for symptoms such as palpitations, pre-syncope or syncope, that are suggestive of an underlying cardiac arrhythmia; **or** Patient is undergoing investigation for the detection of atrial fibrillation following cryptogenic stroke; **or** Patient is planned for AF ablative procedure or

	has already undergone an AF ablative procedure. • Patient is able to understand the nature of the study and able to provide written informed consent. • Patient is willing and able to perform all follow-up visits at the investigational site. • Patient is willing and able to use the CardioMessenger and accepts the BIOTRONIK Home Monitoring concept.
Exclusion criteria	• Patient is implanted with an ICD or pacemaker. • Patient is pregnant or breast-feeding. • Patient is less than 18 years old. • Patient's life-expectancy is less than 12 months. • Patient is participating in another interventional clinical investigation.
Study duration	Sep 2019 – Aug 2021
Sample size	157
Investigational sites	Up to 30
Number of follow-ups per patient	4 (including insertion)
Follow-up scheme	Enrollment – Insertion – 1st follow-up – 48-hour Holter ECG recording* – 3-month follow-up – 12-month follow-up * It is recommended to start Holter recording immediately after the completion of the 1st follow-up procedure (see 9.6).
Coordinating Investigator	[redacted]
Boards (if applicable)	None
Sponsor	BIOTRONIK SE & Co.KG Woermannkehre 1 D-12359 Berlin

3 INTRODUCTION

Implantable Cardiac Monitors (ICMs) are devices which allow cardiac rhythm monitoring for a long time-period. The principal function of these devices is to establish long term continuous cardiac rhythm monitoring to achieve a close correlation between symptoms and arrhythmia.

Typically, ICMs have a retrospective loop memory, which continuously records the most recent minutes of a patient's subcutaneous electrocardiogram (sECG). Data saving of an electrocardiogram can be triggered by three different mechanisms. Most current devices have a patient-activation function, which allows the patient to activate ECG storage (with the help of a user-trigger-device) following a symptomatic episode. Additionally, an auto-detection function allows the capture of arrhythmic events without relying on patient compliance or the perception of symptoms. Finally, a sECG can be captured via a pre-programmed periodic recording.

The most common application of ICMs is the diagnosis of unexplained recurrent syncope. The availability of Implantable Cardiac Monitors has extended the diagnostic opportunities beyond conventional long-term ECGs and the 12-channel ECG. The clinical domain of event recording consists of ECG recording in the case of recurrent syncope of unclear etiology as well as the evaluation of unclear palpitations. Especially with regard to syncope diagnostics, long-term surface ECG achieved a diagnosis in only 4% of patients with syncope even when extended to a duration of 72 hours[1]. It is in this context that ICMs have been utilized and have fast become an important tool in the early stage of the diagnostic approach. ICM insertion is recommended by the current ESC guidelines for the management of patients with syncope[2]. A further application of ICMs is in the detection and management of atrial fibrillation. The detection of AF is crucial in patient populations at high thromboembolic risk and ICMs have been shown to accelerate the detection of paroxysmal AF in this group[3]. This finding has important clinical repercussions. In addition, undiagnosed `silent AF´ is often suspected to be the cause of cryptogenic strokes[4–12]. In patients who have already had a stroke, identification of AF as the cause is critical to initiating proper therapy[13,14]. Early recognition of AF is critical for stroke prevention[15].

Furthermore, ECG monitoring is crucial in assessing the efficacy of rhythm control therapies in patients with established AF. Since AF is often unsymptomatic and the distribution and duration of AF recurrences stochastic, ICMs can objectify the amount of AF. The capabilities of these devices open a wide field of diagnostic potential[16]. The experiences with the second generation of BIOTRONIK's ICM – BioMonitor 2 - since its market introduction in 2015 established the efficacy of its arrhythmia detection software. These well-established software algorithms have now been adopted in the smaller hardware of the BIOMONITOR III.

Like its predecessor ICMs, it is equipped with the Home Monitoring feature, which supports the daily transmission of device stored data including recordings of the subcutaneous ECG triggered by automatic detection, periodic recording or patient activation.

The third generation ICM, BIOMONITOR III, is the subject of this clinical investigation. The most important improvement over its predecessor is its miniaturization while retaining a particularly long sensing vector. This feature will provide large R-wave amplitudes and due to fractal coating of the electrodes and a lossless ECG data compression algorithm improve P-wave visibility, yielding a higher diagnostic value. Miniaturization of the device will improve wearing comfort and allows for an easier, injection-like insertion procedure.

Aims of the study

It is known that the distance between the electrodes of the ICM correlates approximately linearly with the sensing amplitude, supporting the development of longer devices for better signal quality[17]. Nevertheless, the patient comfort is increased with reduced device size. Thus, BIOTRONIK's goal for the third generation of ICM was to develop a device with a substantially reduced device volume than its predecessor BioMonitor 2. With the BIOMONITOR III, the two conflicting goals – reduced device size while maintaining a long sensing vector - were realized with the combination of a rigid and a flexible part of the device body (rigid coated housing-flex lead concept) and the fractal coating of the electrodes (lead tip and distal end of the housing) which is intended to improve signal quality.

Furthermore, the insertion procedure was improved: the new device is inserted via a novel, single insertion tool, onto which it is pre-mounted and therefore insertion has now become a simplified procedure.

This study is a post-market clinical follow-up (PMCF) study to identify and evaluate residual risks associated with the use of the BIOMONITOR III that are discovered or remain even after risk analysis, risk mitigation and successful conformity assessment. Furthermore, this study will also provide additional data as required by regulatory authorities outside of the CE-region.

4 INVESTIGATIONAL DEVICE

4.1 Summary description of the device and its intended purpose

The investigational device used in this clinical investigation is the BIOMONITOR III including the insertion and FIT OneStep insertion tool.

The BIOMONITOR III is a state-of-the-art implantable cardiac monitor (ICM) device intended for monitoring of the heart activity in patients with suspected arrhythmias. The most important cases for ICM use are the diagnosis of a possible arrhythmic cause of syncope, the detection of atrial fibrillation as a cause or precipitating factor for cryptogenic stroke and the management of atrial fibrillation.

4.1.1 BIOMONITOR III

BIOMONITOR III is BIOTRONIK's third generation of ICM which automatically detects and remotely monitors multiple parameters used for diagnosis, early detection or therapy-monitoring of arrhythmic events. The device is not intended to deliver any therapy. [redacted]

The implant device's housing consists of biocompatible titanium which is externally seam welded together and thus hermetically sealed. The implant's ellipsoid shape facilitates subcutaneous insertion.

The BIOMONITOR III system components are available in one variant only. This also applies to the incision and insertion tool as well as to the user-trigger device (Remote Assistant III).

The vector length of an ICM (i.e. electrode spacing) correlates approximately linearly with the sensing amplitude[17]. However, patient comfort increases with reduced device size. In BioMonitor 2, these two opposing goals were realized through the combination of a rigid and a flexible part of the device body, as shown in Figure 1 (left). BIOMONITOR III, which is miniaturized with respect to BioMonitor 2, also follows this approach (Figure 1 - right).

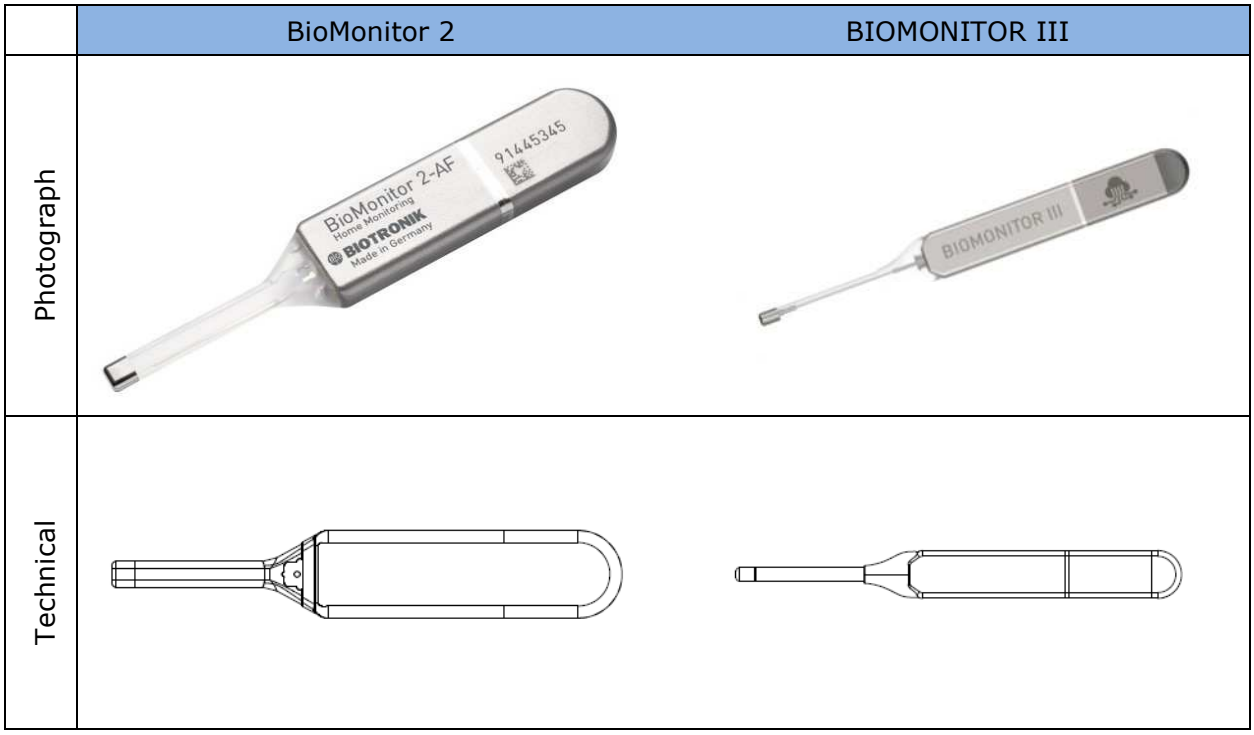


Figure 1: BioMonitor 2 (left) and BIOMONITOR III (right) - BioMonitor 2 and BIOMONITOR III consist of a similar rigid housing and a flexible electrode. BIOMONITOR III is miniaturized compared to BioMonitor 2.

Table 1 gives an overview of the mechanical characteristics of the BIOMONITOR III:

Table 1: Mechanical Characteristics of the BIOMONITOR III.

	L x H x D [mm]	**Volume [cm^3]**
BIOMONITOR III with antenna	77.5 x 8.6 x 4.6	1.9
Housing without antenna	47.5 x 8.3 x 4.3	1.7

The flexible part consists of a silicone lead sleeve with fractal iridium coating over a titanium cap. The rigid part consists of a titanium housing coated with silicone. A small area (25 mm^2) of the housing of the device (on the opposite end to the flexible lead-tip) serves as a sensing electrode and is devoid of silicone coating, having instead a fractal iridium coating. The cardiac signal is derived from the potential difference between the housing electrode and the electrode on the tip of the flexible lead. BIOMONITOR III can adjust itself optimally to the shape of the body due to the combination of rigid and flexible parts. The small width of BIOMONITOR III allows an incision length of only 13 mm, thus reducing the invasiveness of the procedure.

The BIOMONITOR III implant continuously evaluates the cardiac rhythm of the patient using R-R interval based algorithms. Depending on the preset parameters, up to 5 different types of arrhythmias can be automatically detected and documented with corresponding high-resolution sECG recordings and additional episode-related and long-term diagnostic data.

Even in the absence of arrhythmic events, periodic sECGs can be recorded and transmitted to BIOTRONIK's Home Monitoring Service Center (HMSC), as is/was the case with the predecessor devices. The intervals for the periodic sECG recordings can be set through Remote Scheduling programing via the HMSC in BIOMONITOR III.

Diagnostic data and recordings are transmitted via the CardioMessenger external device to the BIOTRONIK HMSC on a daily basis. The selection of sECG recordings is through an intelligent prioritization scheme for storage and transmission. Remote monitoring enables physicians to perform seamless remote diagnostic monitoring and has the potential to spare the patient from unnecessary follow-up visits[24].

Patients with an BIOMONITOR III can safely undergo MRI-scans at 1.5T and 3T without any exclusion zone or any post-insertion waiting time, provided that certain conditions are followed, as fully documented in the BIOMONITOR III device information and the MR Manual[25].

4.1.2 Remote Assistant III

In addition to automatic detections, patients can also trigger a sECG recording when they experience symptoms, using the optional user-trigger device, Remote Assistant III (see section 4.7.2)

4.1.3 Fields of indication

The most important cases for ICM use are the diagnosis of a possible arrhythmic cause of **syncope**, the detection of atrial fibrillation as a cause or precipitating factor for **cryptogenic stroke** and the management of **atrial fibrillation**.

4.1.3.1 Syncope

The ESC guideline for the diagnosis and management of syncope (version 2018)[26] defines syncope as `a transient loss of consciousness (T-LOC) due to transient global cerebral hypoperfusion characterized by rapid onset, short duration and spontaneous complete recovery´[16]. Syncope accounts for 1-6% of emergency room visits and about 1% of hospital admissions[27]. The burden on the patient from recurrent syncope is comparable to that in chronic illness and has serious effects on their quality of life. While it occurs intermittently, its threat of reoccurrence continuously impairs quality of life. Since more than half of the general population complains of an episode of T-LOC during life, syncope is extremely frequent in the general population.

According to the guidelines there are multiple principal causes of syncope which are classified in three main groups[27]:

- reflex syncope
- syncope due to orthostatic stress
- cardiac syncope

Cardiac arrhythmias, such as bradycardia, tachycardia and drug induced arrhythmias are the most common causes of cardiac syncope.

Syncopal events are transient, often unwitnessed, have a sporadic nature and their recurrence period cannot be predicted. Furthermore, as described above, syncope has multiple possible underlying causes. Taken together, these features of syncope lead to difficulties in standardizing diagnostic procedures. Therefore, the opportunity to record a specific ECG at the time of syncope is very difficult to achieve, and this explains the low diagnostic yield of Holter ECG recording for the majority of syncope patients: 4%-35%, depending on the monitoring time and frequency of syncopal events in the individual patient. The correlation between cardiac arrhythmias and symptoms is crucial for diagnosing syncope of cardiac etiology. As a consequence, prolonged cardiac rhythm monitoring is a logical approach for ruling out or confirming arrhythmogenic syncope. The ability of ICMs to continuously record ECGs over a long period of time when activated either by the patient (usually after symptoms) or automatically in case of occurrence of pre-defined arrhythmias, increases the likelihood of symptom-ECG correlation for patients with infrequent and transient symptoms recurring over months. This also may explain the high diagnostic yield of ICMs in comparison with `conventional´ investigations like tilt table tests, EP studies or adenosine triphosphate tests. For these reasons, ICMs are becoming increasingly important in guiding a safe, specific and effective therapy for patients with unexplained and recurrent syncope and should be inserted early rather than late for the evaluation of unexplained syncope[28]. ICMs can be safely inserted in the initial phase of the diagnostic evaluation of recurrent unexplained syncope patients and are highly effective to guide a specific therapy based on the documented ECG findings.

4.1.3.2 Crypogenic stroke

Approximately one in five ischemic strokes is associated with AF[29]. In addition, undiagnosed `silent AF´ is often suspected to be the cause of cryptogenic strokes[4–12]. In patients who have already had a stroke, identification of AF as the cause is critical to initiating proper therapy[13,14]. Early recognition of AF is critical for stroke prevention[15]. Clinical guidelines recommend that patients with cryptogenic stroke take antiplatelet agents to prevent recurrence. However, when AF is detected, guidelines recommend oral anticoagulation because their increased risk of bleeding complications is outweighed by the marked superiority over antiplatelet drugs for preventing recurrent stroke in this population[30–32]. The routine use of cardiac monitoring to identify patients with paroxysmal AF who will benefit from anticoagulation has been reported to be cost-effective[33].

4.1.3.3 Atrial fibrillation

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice, accounting for approximately one third of hospitalizations for cardiac rhythm disturbances. An estimated 2.3 million people in North America and 4.5 million people in the European Union have paroxysmal

or persistent AF[34]. The prevalence of AF increases with age, from <0.5% at 40–50 years, to 5–15% at 80 years[29].

AF is associated with increased rates of death, stroke, non-stroke related thromboembolic events, heart failure, hospitalizations, impaired quality of life, reduced exercise capacity, and left ventricular dysfunction[29,29,34,35]. Various factors[36], including rapid or slow heart rates, irregular heartbeats, and the loss of the atrial contraction (`atrial kick´) to ventricular filling can contribute to the development of AF symptoms such as palpitations, fatigue, dyspnea, dizziness, chest pain, and syncope. However, symptoms are neither a sensitive nor a specific sign of AF, because there is a poor correlation between symptoms and arrhythmia. Therefore, relying only on symptoms to drive therapies for AF can be very misleading. Objective measures for AF detection, based on ECG recording(s), are currently endorsed by all clinical guidelines regarding AF management[16,29,34,37–40].

AF detection may utilize intermittent or continuous monitoring. Available intermittent monitoring methods include standard ECGs, Holter recorders (24-hour to 7-day), trans-telephonic ECGs, and external event recorders with or without loop memory. Continuous AF monitoring is feasible however, through the utilization of ICMs[18]. It is well established that the more intensively a patient is monitored and the longer the period of continuous monitoring, the greater the likelihood of detecting both symptomatic and asymptomatic AF[41–52]. Therefore, especially to assess freedom from AF, continuous ECG recording is the gold standard[38,53–55].

Therapeutic strategies for AF may be preventing thromboembolism, minimizing symptoms, restoring sinus rhythm, and controlling the ventricular rate[3929,34]. While antiarrhythmic drug therapy remains the first-line treatment for AF in the majority of patients, the ablation therapy for treatment of AF has gained wider acceptance due to steadily improving efficacy[56]. However, since many AF episodes are asymptomatic, and AF recurrences are often clustered and do not show a random pattern[16,38,57], the efficacy of AF therapy may be over-estimated by using intermittent or short-term ECG monitoring techniques. Moreover, AF may reoccur very late after a long-lasting (> 1 year) episode-free time period in patients treated with AF ablation. Therefore, to objectively compare success rates of different therapeutic procedures to reestablish sinus rhythm continuous and long term ECG monitoring is needed[16,29,34,37–39,58–61].

4.2 Manufacturer

The manufacturer of the BIO|MONITOR III 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

The device undergoing clinical investigation is BIOTRONIKs BIOMONITOR III including the Incision Tool and Insertion Tool (FIT OneStep):

Model Name	Model Number
BIOMONITOR III including Incision Tool and Insertion Tool (FIT OneStep)	[redacted]

In addition, the following BIOTRONIK devices will be used during the investigation and undergo clinical investigation as additional device of interest:

Model Name	Model Number
ICS 3000 programmer device (or successor)	[redacted]

Model Name	Model Number
Renamic programmer device (or successor)	[redacted]
Programmer software PSW1901.A/1 (or successor versions)	[redacted]
Remote Assistant III (or successor)	[redacted]

Furthermore, the following BIOTRONIK devices will be used during the investigation:

Model Name	Model Number
CardioMessenger II	[redacted]
CardioMessenger II-S	[redacted]
CardioMessenger Smart 2G CE (or successor)	[redacted]
CardioMessenger Smart 3G CE (or successor)	[redacted]
CardioMessenger Smart 3G AU (or successor)	[redacted]

Throughout the Master study conduct, data on used BIOTRONIK accessories (additional devices) may be collected, as required to support regulatory requirements. All devices used within the scope of this Master Study are CE certified. Participating sites outside of the CE area will only use the devices after market approval or approval for the Master Study by the respective regulatory institution according to national regulations.

Note: The BIOMONITOR III as well as Remote Assistant III are not yet listed on the Australian Register of Therapeutic Goods (ARTG). The study will be conducted under the CTN (Clinical Tial Notification) scheme in Australia. The devices provided to the investigators at Australian sites will be labelled as investigational devices and must not be used in routine care until TGA approval.

4.4 Description of traceability

Every BIOMONITOR III has an 8-digit serial number. The traceability is assured due to recording of serial numbers and patient ID during the insertion procedure. Moreover, this information is documented on the corresponding electronic case report form (eCRF) and recorded in the clinical data management system (CDMS) enabling to create a list with all used devices within the study.

All devices used in this clinical study carry a CE mark and will be used within their intended use. A device accountability log (DAL) will be used in countries which are not CE certified as described in section 15. The traceability is assured by a process which records the shipment, receipt, storage, usage, transfer and/or return of used, unused or malfunctioned investigational devices in the DAL. Device information as model name, 8-digit serial number, date of shipment or return, UBD, shipment destination and usage is entered in the DAL via the CDMS. Investigational devices shall be stored in locked cabinets or rooms separated from non-investigational devices. Only trained BIOTRONIK personnel or trained site personal is authorized to have access and to handle investigational devices. A list of approved local personal is kept at each study site, respectively.

Explanted or malfunctioning devices shall be sent back to the manufacturer. The investigator shall contact the respective sales representative in order to organize shipment.

4.5 Intended purpose of the device in the study

The BIOMONITOR III system and all other devices (see section 4.3) will be used in this study according to their intended use. The BIOMONITOR III is an implantable cardiac monitor that records subcutaneous ECGs. Recording is activated both automatically and by the patient.

The device is housed in the front part of the FIT OneStep insertion tool (Fast Insert Tool). The insertion tool is used for forming the device pocket and for subsequent positioning of the cardiac monitor in the subcutaneous left pectoral area. The use of this tool ensures an optimal anatomical implantation site, which is a requirement for recording meaningful subcutaneous ECGs.

Note: The BIOMONITOR III does not have any therapeutic function.

4.6 Intended patient population and indications

The intended patient population consists of all patients who would benefit from long-term cardiac rhythm monitoring.

4.6.1 Indications of BIOMONITOR III

Generally approved differential diagnostic methods, as well as the indications and recommendations for the medical use of implantable cardiac monitors apply to the BIOMONITOR III. BIOMONITOR III is an insertable patient-activated and automatically–activated monitoring system that records subcutaneous ECG (sECG). The primary purpose is to provide early detection and diagnostics in the following clinical scenarios:

- Clinical syndromes, which lead to an increased risk of cardiac rhythm disturbances
- Temporary clinical symptoms, including dizziness, palpitations, syncope, or chest pain, which maybe the result of a cardiac rhythm disturbances
- Evaluation of palpitations of unclear etiology
- Recurrent syncope of unclear etiology
- Confirmation or monitoring of atrial fibrillation
- Clarification of a cryptogenic cerebrovascular stroke

1.1.1 Contraindications of BIOMONITOR III

There are no known contraindications for the insertion of BIOMONITOR III. However, the particular patient's state of health determines whether a subcutaneous device will betolerated permanently.

4.7 Description of the investigational device

4.7.1 BIOMONITOR III

BIOMONITOR III represents BIOTRONIK’s third generation of Implantable Cardiac Monitor (ICM) systems. BIOMONITOR III continually monitors the incoming cardiac signals and applies various automatic detection criteria, which are all based on R-R interval analysis.

Programmable parameters allow to patient-individually adjusting the implant for diagnosis, early detection or therapy monitoring. The device is not intended to deliver any therapy.

The implantable cardiac monitor BIOMONITOR III is premounted onto the FIT OneStep insertion tool. The assembly is provided in a single blister, together with an incision tool. For materials with body contact, refer to 4.1.1.

Via the optional Remote Assistant III, the recording of subcutaneous electrograms (sECG) can be triggered by the patient in case of symptomatic episodes.

It should be understood that the BIOMONITOR III does not make rhythm diagnosis. It is designed to detect suspicious rhythm segments and store their sECG to allow the physician to decide if an arrhythmia was present. For example, a detection of `high ventricular rate´ can be normal sinus rhythm during exercise, a ventricular or supraventricular tachycardia, or atrial fibrillation with rapid conduction. The device will record rhythm segments depending on the programming; `true´ arrhythmias (such that the physician wanted to detect) may remain

undetected and `false´ detections (such that the physician did not want to detect) may be recorded. It is the task of the user to program the device according to the indication of the patient and the respective `costs´ of under- and over-detection.

4.7.1.1 sECG sensing and noise

The BIOMONITOR III features a combination of a rigid and a flexible part of the device body as shown in Figure 2 below. The total device length is 77.5 mm. The overall device length defines the sensing vector of the ICM (i.e. electrode spacing) and correlates approximately linearly with the sensing amplitude. The rear end of the housing, as well as the lead tip, constitute the ICM's sensing electrodes and are fractally coated with iridium.

The flexible part consists of a silicone lead body and a titanium cap and contains the electrode which also serves as the Home Monitoring antenna. The rigid part consists of titanium housing and is coated with silicone.

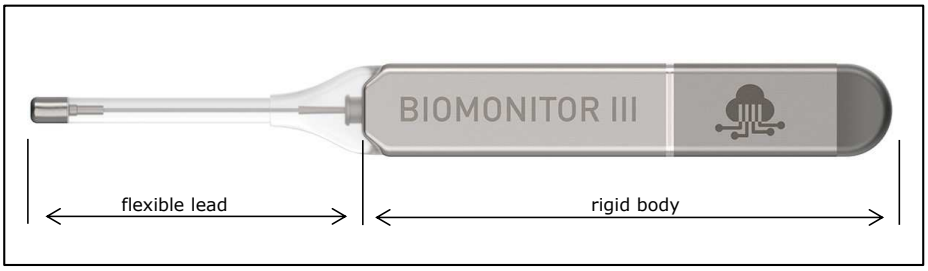


Figure 2: BIOMONITOR III shape and sensing vector.

The shape of BIOMONITOR III allows placement in a parasternal position, which is closer to the heart than a typical pacemaker pocket and has been shown to result in increased amplitudes of the sensed cardiac signals.

The fractal coating of the electrodes, a low high-pass filtering and a lossless compression algorithm for the storage of the subcutaneous electrocardiogram (sECG) provide for improved signal quality.

BIOMONITOR III continuously monitors the cardiac signal by detecting the R-waves and evaluating R-R intervals for arrhythmia detection:

[redacted]

For recordings (device memory and transmissions via HomeMonitoring), the unfiltered signal is stored as it contains more information for diagnostic purposes, in particular P-waves.

During an in-office follow-up, both signal channels can be displayed simultaneously in real-time. The amplitudes of the unfiltered R-waves are measured automatically and annotated beside the corresponding signals. Furthermore, daily means for R-wave amplitudes and percentage noise/day are stored as long-term trends.

The parameters for the sensing settings, such as sensing and high pass filter, sensing parameter sets (SensingConsult) etc. can be adjusted individually for each patient. The sensing parameter sets are accessed via the feature SensingConsult. There are 5 preconfigured sensing programs addressing the most common signal challenges evolving from T/P-wave oversensing and signal amplitude variations due to VES.

4.7.1.2 Asystole detection

BIOMONITOR III detects asystole when the interval between the current and the previous sensed ventricular events (Vs) is longer than the programmed asystole interval limit. The asystole interval limit can be programmed in the range from 2 to 10 seconds in steps of one second. The default value is 3 seconds. When an asystole is detected, typically 60 seconds (minimum 40 seconds) of ECG will be stored in the device memory.

4.7.1.3 Bradycardia detection

BIOMONITOR III detects bradycardia when the average rate of sensed intervals (Vs) over a programmed duration is less than a programmed rate limit. The rate limit can be programmed in the range from 30 to 80 bpm in steps of 5 bpm. The duration can be programmed from 5 to 30 seconds in steps of 5 seconds. The default values are 40 bpm for duration of 10 seconds. When a bradicardia is detected, typically 60 seconds (minimum 40 seconds) of ECG will be stored in the device memory.

4.7.1.4 Sudden Rate Drop detection

Sudden Rate Drop is detected in BIOMONITOR III when the rate decreases by a programmed percentage. The change in rate is measured by comparing a pre-interval average and a post-interval average. There are several parameters which allow adjustment of the Sudden Rate Drop trigger for each patient individually. The Sudden Rate Decrease can be programmed to 20 %...(10 %)…70 % of the pre-interval average, and the default is `Off´; the number of intervals used in the pre-interval average (Base line intervals) can be programmed to 48, 64, 128, 256, with a default of 64, and the number of intervals used in the post-interval average can be programmed to 8, 16, 32, with a default of 16.

When Sudden Rate Drop is detected, typically 60 seconds (minimum 40 seconds) of ECG will be stored in the device memory. This ECG trigger criterion is not offered by any of the competitors.

4.7.1.5 High ventricular rate detection

BIOMONITOR III detects a high ventricular rate (HVR) whenever the rate increases above a programmed rate limit for a programmed number of sensed intervals. For detection of HVR an up/down counter is used. Each ventricular sensed interval that has a rate greater than or equal to the programmed rate limit increases the counter. Each ventricular sensed interval that has a rate below the programmed rate limit decreases the counter. The HVR limit can be programmed in the range from 100 to 200 bpm in steps of 10 bpm; the default rate is 180 bpm. The up/down counter threshold can be programmed to 8, 12, 16, 20, 24, 32, 64; the default value is 16. When the counter exceeds the programmed threshold, an HVR event is registered. When HVR is detected, 60 seconds of sECG will be stored in the device memory. The HVR event is considered as terminated when the rate is below the programmed rate limit for a programmed number of consecutive sensed intervals.

4.7.1.6 Atrial fibrillation detection

BIOMONITOR III detects atrial fibrillation in case of irregular ventricular rhythm. The BIOMONITOR III AF detection algorithm identifies both the onset and termination of an AF episode by analysing the stability of the inter-beat (R-R) intervals, which are generated from the QRS detection in the subcutaneous ECG.

Briefly, the algorithm continuously evaluates the stability of R-R intervals in moving analysis windows. The stability of R-R intervals is assessed by calculating the differences between consecutive pairs of R-R intervals which are related to the mean R-R intervals within the analysis window and compared with a programmable stability threshold.

Differences between R-R intervals exceeding the stability threshold are considered unstable, and in case the programmable number of unstable intervals within the analysis window is

reached, the window is considered unstable as a whole. AF is preliminarily detected when a programmable number of consecutive analysis windows are found to be unstable. If the preliminary AF status is sustained over a programmable confirmation period, then the AF is confirmed and the previously recorded AF-detection recording is stored and AF statistics are updated. The algorithm identifies the AF termination in a similar way, but with a separate set of programmable parameters. The recognised termination of an AF triggers another ECG recording.

The physician's programmer providers a user interface through which the AF detection function can be turned ON or OFF, and the AF sensitivity can be selected from predefined settings (low, medium, high) or individual configuration. The latter allows expert customization of AF detection or termination parameters including: AF confirmation period, R-R variability limit, number of detection/termination windows, detection intervals, and termination intervals.

4.7.1.7 Bigeminy rejection

The bigeminy rejection parameter of the AF detection algorithm attempts to filter out two, three and four interval repeatable premature atrial contractions (PAC) and/or premature ventricular contractions (PVC) patterns from AF detection. Bigeminy rejection sensitivity has three settings: off, standard and aggressive. When Bigeminy rejection is off, irregular but periodic patterns are not rejected from AF detections. With the `Standard´ setting, the algorithm rejects bigeminy rhythms that are relatively stable and repeatable. However, in some patients who are not in AF, the pseudo-irregular intervals during geminy show a less obvious repeating pattern, as also for instance during transitions between different states of bigeminy (bigeminy, trigeminy or quadrigeminy). In these patients, the `Aggressive´ setting may be used to filter out these rhythms more consequently and avoid false positive detection of AF.

4.7.1.8 sECG episode saving and diagnostic statistics

The BIOMONITOR III is equipped with a loop memory that can store at least 60 minutes of recordings. Each automatically detected AF episode is records for typically 60 seconds subcutaneous ECG (minimum 40 seconds), consisting of typically 50 seconds pre-trigger (minimum 30 seconds) and exactly 10 seconds post-trigger data. If memory volume has been used up, an overwrite algorithm becomes effective. However, the BIOMONITOR III will always save the oldest and the newest AF recordings, as well as the recording corresponding to the longest AF episode detected by the device.

The BIOMONITOR III provides comprehensive AF diagnostic statistics to facilitate arrhythmia management, including: the number of AF detections, the percentage of time spent in AF (AF burden), and the length of the longest AF episode. The BIOMONITOR III also generates AF start time-of-day and AF duration histograms to reveal the temporal distribution of the AF episodes. In addition, BIOMONITOR III tracks the progression of AF by trending display of the AF duration per day, number of AF episodes per day, mean heart rate during AF, and max heart rate during AF.

In the monocenter clinical `AF Detect´ study the performance of the AF detection was investigated. The study demonstrated good AF detection performance.

4.7.1.9 Indication specific program sets

BIOMONITOR III offers four pre-configured parameter sets which tailor the arrhythmia detection-settings with respect to sensitivity and specificity to the four most prominent indications: Syncope, palpitations, AF monitoring and cryptogenic stroke. This feature is called ProgramConsult and is accessed via the programmer.

These indication-based programs also impact the configuration of sECG-recordings and HomeMonitoring transmissions.

4.7.1.10 Insertion of the BIOMONITOR III

BIOMONITOR III has been developed to be inserted in a close-fitting subcutaneous tunnel, preferably in or around the left side of the chest. Recommended locations are areas close to the heart, where minimal device movement due to positional changes or body and arm movement is expected (Figure 3). The investigator determines the insertion site in accordance with the individual patient anatomy and comfort, cosmetical considerations, and possible diagnostic measures in the future (e.g. mammography). Potential positions for the insertion of the BIOMONITOR, including those that are not provided in the IFU (D-F), are illustrated in Figure 3.

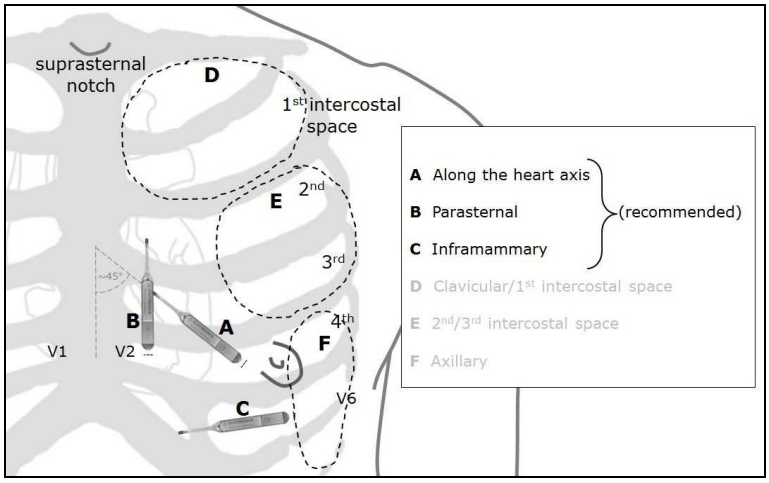


Figure 3: Potential positions of the BIOMONITOR III.

The choice of placement location is to be decided by the physician, on the basis of individual patient anatomy and comfort, as well as cosmetic considerations and diagnostic measures potentially necessary in the future, e.g. mammography.

Note: It is strongly recommended to consider patient anatomy carefully, e.g. the effect of forces of moving tissue mass on the implanted device. The lead tip can be positioned upward or downward, considering patient-specific as well as cosmetic aspects: The subcutaneous electrocardiogram can also be displayed reversed by appropriate programming.

Local anesthesia:

Local anesthetic agent is injected at the selected anatomical position, both along the incision line, and along the length of the planned tunnel. An appropriate delay is allowed to let the local anesthetic agent take effect before the insertion procedure is continued.

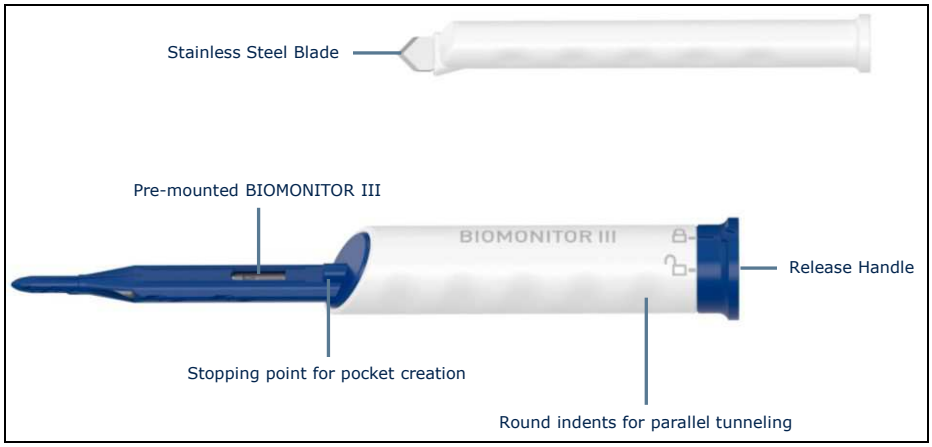


Figure 4: Incision tool and FIT OneStep insertion tool (with premounted device).

Incision procedure:

Local anesthetic agent is injected at the selected anatomical position, both along the incision line, and along the length of the planned tunnel. An appropriate delay is allowed to let the local anesthetic agent take effect before the insertion procedure is continued.

Note: It should be made sure that local anesthesia guarantees proper numbing of the complete tunneling length [redacted] by using at least two injections.

The Incision tool has a blade of stainless steel [redacted] (Figure 4) and is used to make a ~13 mm wide incision through the skin. The skin should first be pinched to raise a skin fold perpendicular to the tunneling direction and the tool-blade pushed in at approximately 90° to the raised skin fold (Figure 5). The incision depth is limited to 10 mm by design.

The following advices should be considered:

- Ensure the tool blade is pushed in at 90° to the skin to create a clean vertical cut.
- Vertical cut can be achieved in multiple ways – pinching the skin minimizes the risk of undesirable muscle damage and protects the ribs.
- A vertical cut minimizes bleeding, simplifies wound closure and allows for cosmetic healing.

Insertion procedure:

The FIT OneStep insertion tool allows an injection-like insertion of the implant using a single tool (Figure 4). It is used for forming the device tunnel and subsequent subcutaneous positioning of the BIOMONITOR III implant in the left pectoral area.

The BIOMONITOR III implant is premounted into the tunneling end of FIT OneStep tool (Figure 4). The FIT OneStep tool is inserted in the incision opening and then advanced within a sub-dermal plane (e.g. subcutaneous fat-layer) parallel to the skin at a depth of approximately 5mm until the tool handle approaches the skin incision, to create a tunnel for the BIOMONITOR III implant (Figure 6, upper row). It is important to bring the FIT OneStep into a parallel position to the body surface and not at an angle as inserting at an angle may result tunneling into the muscle. The handle should be held with the fingers at the side of the handle. This allows a very controlled and parallel tunneling process. Advance the FIT OneStep all the way to the blue stop at the handle. This places the device ~10mm away from the incision. Once the tunneling part of the tool is fully inserted, a knob at the proximal end of the handle is turned in order to release the placement-mechanism. A noticeable "click" indicates that the tool is unlocked. Whilst keeping the white handle in place with one hand, the tunneling end of the tool is pulled back by the blue knob at the proximal end and fully retracted through the outer handle of the tool. The knob is pulled in a linear fashion away from the white handle. As a result, the clam-shell tunneling tip of the tool is pulled back over the implant, leaving the implant within the subcutaneous tunnel (Figure 6, lower row).

It is important to keep the handle in place with the tool fully inserted to the stop, when operating the release-knob and during withdrawal of the tunneling part of the FIT OneStep tool.

Note: To ensure sufficient tunneling length, attention should be paid to fully advance the insertion tool to the tool stop-point and to keep the tool handle in place during unlocking and retraction of the inner part of the tool.

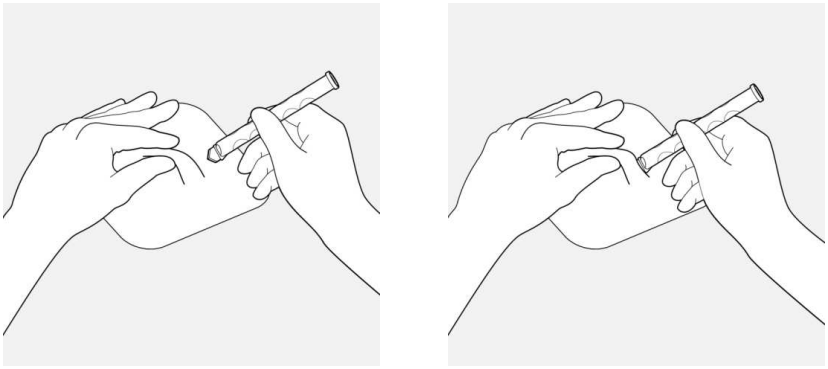


Figure 5: Insertion procedure: Handling of the incision tool.

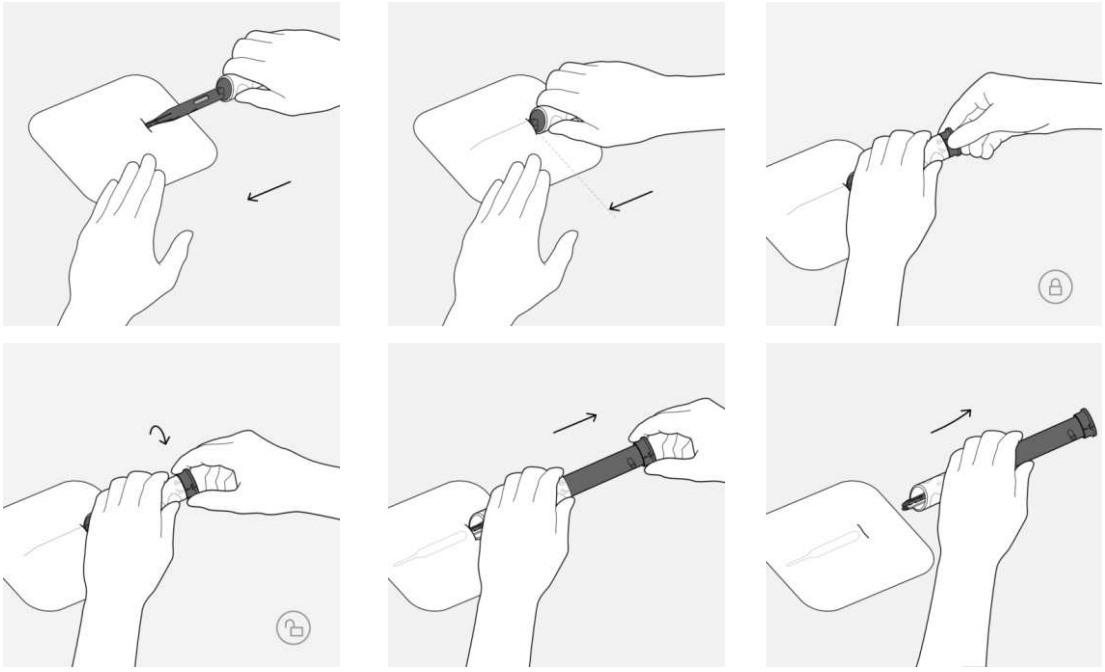


Figure 6: Insertion procedure: Handling of FIT OneStep and placement of BIOMONITOR III.

For incision closure, standard clinical practice is advised. It might be of potential advantage for certain patients (e.g. obese) to have 1-3 deep tissue sutures for device fixation and a subdermal suture for wound closure (e.g. interdermal continuous suture). The protection of the wound from environmental influences, according to hospital guidelines, finalizes the insertion procedure of BIOMONITOR III.

Note: Difficult patient anatomies, which exert elevated forces on the implanted device might require extensive wound closure, i.e. the application of a continuous intradermal suture and 2-3 deep sutures.

4.7.1.11 BIOTRONIK Home Monitoring, ReportShare and Patient App

The BIOTRONIK cardiac monitors provide a complete diagnosis management system:

With **Home Monitoring**, diagnostic information as well as device technical data are automatically and wirelessly sent to a stationary or mobile transmitter (CardioMessenger Smart) via an antenna in the lead body. The data are encrypted and sent from the transmitter to the BIOTRONIK Home Monitoring Service Center (HMSC) through a cellular phone network.

Note: The usage of the Home Monitoring system is mandatory in the BIO|MASTER.BIOMONITOR III study.

Data collected during in-office follow-ups on the programmer can also be uploaded to the HMSC using the ReportShare function of the programmer. **ReportShare** is a software that allows the physician to upload follow-up data interrogated during an in-office follow-up to the HMSC by using a UMTS-capable Renamic programmer and a cellular phone network connection. The received data are deciphered and evaluated. Each physician can set the criteria for evaluation to be used for each patient and can configure the time of notification within the HMSC.

A clear overview of the results of this analysis is displayed for the attending physicians on the protected Internet platform (HMSC) and can be exported in a PDF-format (`StatusReport´).

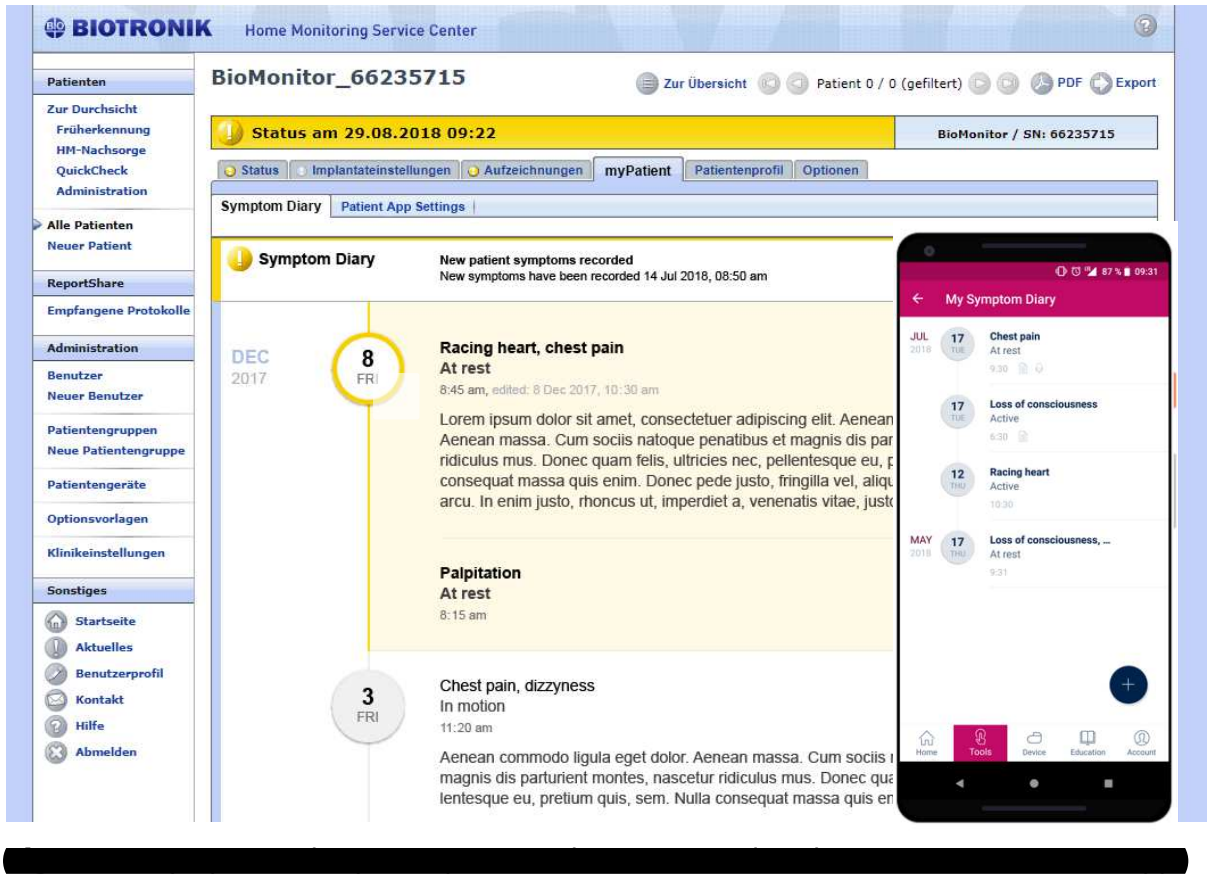
Data transmission from the device is performed with a daily device message. Device messages that indicate special cardiac-related events or technical events are uploaded at the pre-set time. A test message can be initiated at any time using the programmer to immediately check the Home Monitoring function.

Important medical information includes the following:

- Atrial arrhythmias
- Ventricular arrhythmias
- Current statistics
- Periodically recorded subcutaneous ECGs that are transmitted according to an individually adjustable timing interval in addition to the regular device message

For documentation of medical symptoms, the patient has the option to download the BIOTRONIK **Patient App** for use with a private smartphone. The Patient App software provides a symptoms diary in which the patient may describe the exact time of occurrence, nature and duration of medical symptoms (see Figure 7). Data of the symptom diary will be transmitted via cellular networks to BIOTRONIK and will be made available to the investigator via the BIOTRONIK Home Monitoring Service (see above). The symptom diary may therefore ease the workflow for the investigator and increase the diagnostic yield. However, HomeMonitoring and the Patient App software **are no emergency systems.** In the event of an emergency or disturbances, the patient is asked to seek medical care and go to available medical facilities.

Note: We strongly recommend using Report Share to facilitate the data transfer. The usage of the Patient App system is not mandatory in the BIO|MASTER.BIOMONITOR III study.



4.7.2 Remote Assistant III

The patient-triggered recording is particularly relevant in the following scenarios:

- In case of typical symptoms like dizziness or palpitations
- After syncope or pre-syncope.

In BIOMONITOR III this functionality is realized, as with the predecessor BioMonitor 2, by a small electronic user-device, the Remote Assistant III.

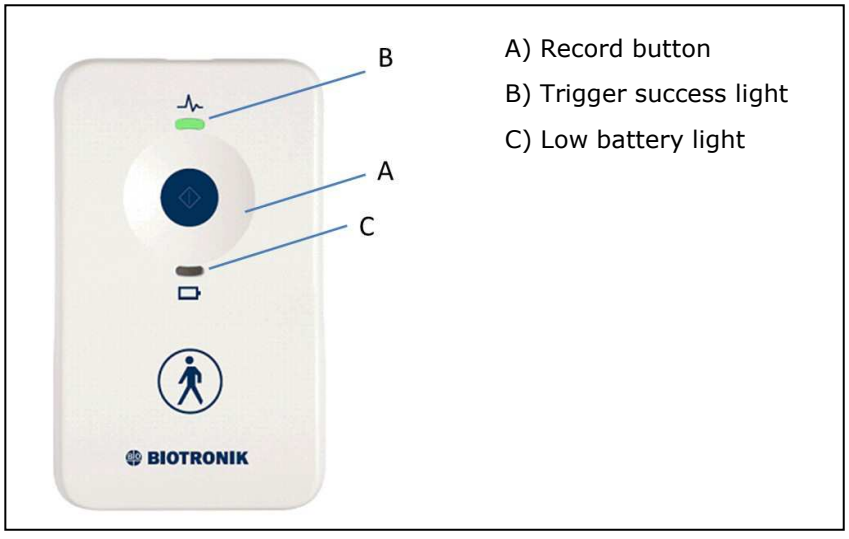


Figure 8: Remote Assistant III patient-trigger device.

The Remote Assistant III user-device is a hand-held, battery-operated device which uses radio-frequency and coil telemetry to communicate with the BIOMONITOR III implant. The Remote Assistant III is intended for unsupervised use away from a hospital or clinic. The Remote Assistant III activates the data management features in the BIOMONITOR III to initiate recording of cardiac event data in the inserted device memory. Remote Assistant III (Figure 8) has a single, user-operated button located in the middle of the device.

Remote Assistant III provides the user with the ability to activate the storage of an SECG when a symptomatic event occurs or has occurred by applying the device over the location of BIOMONITOR III, and pressing the record button (position A in Figure 8). After the record button has been pressed, the Remote Assistant III indicates by an audible tone if the button has been pressed sufficiently. If communication with the inserted device was successful a steady green light is shown by the light indicator. A blinking yellow light on the other hand would indicate that communication has failed and the trigger-command has not reached the BIOMONITOR III (position B in Figure 8). In such a case, the patient is supposed to check the position of the Remote Assistant III over the implanted BIOMONITOR III before trying again. A second indicator light on the Remote Assistant III (position C in Figure 8) indicates if its battery voltage is low.

Note: For the pupose oft the study it is not mandatory that a Remote Assistant III is permanently handed over to the patient.

4.8 Summary of training and experience needs

BIOMONITOR III is a medical implant intended for medical staff who are familiar with the insertion of implantable cardiac monitors. In addition to having basic medical knowledge, the user must be thoroughly familiar with the operation of the implantable cardiac monitor and the specified conditions for its use. Only qualified medical personnel is permitted to insert the BIOMONITOR III and make a diagnoses. Therefore, participants will be trained by a qualified representative of the sponsor or other already trained medical staff on the BIOMONITOR III handling and insertion. As the BIOMONITOR III is new to the market, during the initial insertions in this study, a representative of the sponsor or trained implanting physician should be present to give advice if needed. The handling and insertion procedure are described in a respective function manual.

The interrogation and programming of BIOMONITOR III shall only be done by appropriately trained personnel and using a BIOTRONIK programmer with appropriate programmer-software. Furthermore, the study teams need to be familiar with the Home Monitoring functionality. The BIOMONITOR III measurements should be continuously observed by the investigator via the Home Monitoring functionality.

4.8.1 Description of medical and surgical procedures

BIOMONITOR III has to be inserted by medical staff following the standard insertion procedure, according to the current instructions for use (IFU). Specific information pertaining to procedures is provided in the respective technical manuals. The care-taker must be familiar with the associated risks and complications.

After completion of the insertion procedure, the implanter will perform wound closure and prevention of infections according to the local clinical practice (4.7.1.10).

In accordance with the technical manual of the BIOMONITOR III, 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

Results of pre-clinical and clinical data of the predecessor BioMonitor 2 and the investigational device BIOMONITOR III are summarized below. The proven algorithms of BioMonitor 2 have been adopted in BIOMONITOR III as previously discussed.

5.1.1 Animal study

An animal study was carried out with the primary objective of ensuring that BIOMONITOR III demonstrates an acceptable level of safety before starting the First-in-Man Study BIO|CONCEPT.BIOMONITOR III. Safety was addressed by evaluation of the insertion procedure, evaluation of the grown-in of the device, and evaluation of migration. In addition QRS detection performance was assessed at insertion and at six weeks after insertion.

A total of six Yucatan swine were used in this study. All swine received two devices each – one BioMonitor 2 and one BIOMONITOR III, thereby reducing the total number of animals required to perform the study and increasing the correlation of the data. Details of the study design, data acquisition, endpoints and results are described in detail in the 'Preclinical Study Report Summary: Assessment of the BIOTRONIK BIOMONITOR III Utilizing a swine model[62] [MSEI, 2019]. The conclusions of the study are as follows.

The six-week chronic BIOMONITOR III implant study in swine passed the safety endpoints which consisted of insertion procedure evaluation, grow-in device evaluation, and migration evaluation. All three experienced physician-implanters awarded a score of 4.0 (maximum score, indicating very good performance) to the BIOMONITOR III incision tool, FIT OneStep insertion tool, and overall device performance. Four aspects of the insertion site were evaluated six-weeks after insertion including redness at the insertion site, redness of surrounding tissue, signs of tissue erosion and elevation of local tissue temperature relative to adjacent tissue. Each BIOMONITOR III and BioMonitor 2 device insertion site received a score of 4.0 (very good) signifying that no issues were observed and the insertion site conditions were acceptable. Migration was observed in for one BIOMONITOR III device and one BioMonitor 2 device. The BIOMONITOR III device migrated approximately 2 cm cranial relative to the initial insertion location. The BioMonitor 2 migrated approximately 3 cm caudal to the initial insertion location. Migration in both devices did not result in QRS signal degradation. QRS detection performance achieved 100% sensitivity and 100% PPV in all devices at insertion and prior to sacrifice.

During week 2 data collection, the Renamic programmer was unable to communicate with the BIOMONITOR III device of one subject. This communication issue was resolved due to a software update which was completed outside of the scope of the study.

This animal study found no safety issues related to the BIOMONITOR III tools and device as well as equivalent QRS detection performance between BIOMONITOR III and the predicate BioMonitor 2 device.

5.1.2 Usability study

This validation study investigated the safety and performance of the Incision Tool and preloaded Insertion tool (FIT OneStep) by use of cadaver testing on 25th to 26th of September 2018. Cadaver testing of ICM insertion is a method through which clinical tools can be tested with respect to their clinical performance. The cadaver study to support BIOMONITOR III FIT tools is similar to the cadaver study that was used to support BioMonitor 2 clearance (K152995, Appendix 31: VER-111-14-3385).

Fifteen physicians, all experienced ICM users (i.e., 20+ insertions per year for 3+ years), were recruited to participate in this validation study. Each participant completed four successful device insertions, for a total of 60 insertions.

The success criteria for this study were defined as the following:

- No use errors or close calls shall be identified as this result of this study.
- No additional hazard-related scenarios shall be identified as this result of this study.

Failure of one or more of these criteria shall require further design mitigation and potentially additional testing, depending on the results of study and the changes necessary.

The simulated use testing took place in a surgical operating room, where human cadavers functioned as models for live humans. Test observers watched as physicians completed their tasks evaluating the safety and usability of the Incision Tool, Fast Insertion Tool (i.e., FIT OneStep), IFU, and non-verbal reference guide for the insertion procedure.

The physicians were asked to open and remove the contents from the BIOMONITOR III package and to define and create an incision for inserting the BIOMONITOR III. Physicians successfully completed every task with no use errors, close calls, or use problems observed by the test observers.

After the tasks were complete, test observers conducted interviews to confirm their observations and to learn about any of the implanters' thoughts or concerns surrounding the tooling or instructional materials. No safety-related concerns were identified as a result of these interviews. Therefore, no additional risk analysis was necessary and no device or tooling design changes were required as a result of this human factors validation test.

5.2 Clinical data

For the BIOMONITOR III, six clinical studies contribute to the evaluation of clinical data:

- BioMonitor Master study
- Single-center AF Detect study
- BioMonitor 2 Pilot study
- BIO|MASTER.BioMonitor 2 study
- BioInsight
- BIO|CONCEPT.BIOMONITOR III

The following chapters describe the above mentioned studies and analysis in more detail.

5.2.1 BioMonitor Master Study[1]

The objective of the BioMonitor Master study (NCT01725568) was to confirm the safety and efficacy of BioMonitor (first generation ICM) and to collect PMCF data. 152 patients were inserted in 17 clinical sites in 6 countries. The first patient was recruited on October 31, 2012, last patient out was on October 10, 2014. The observation time was one year. No device related and 4 procedure related serious adverse device effects (SADE) occurred. 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) lower than 90% (Min 85.5%). The mean value of the R-wave amplitude was 0.3 mV over the study observation time. The overall performance of the implantable cardiac monitor BioMonitor was within the expected range. Therefore, BioMonitor was evaluated as safe and efficacious.

[1]Clinical Investigation Report of the BIO|Master.BioMonitor study of the Implantable Cardiac Monitor BioMonitor, Version 1.0. 2015

5.2.2 Single-center AF Detect study[2, 3]

This single-center clinical study was performed with inserted BioMonitor devices in order to assess the performance of the AF detection feature in clinical practice. 66 patients were enrolled. The first patient was recruited on November 21, 2013. Last patient out was on July 1, 2014.

The ability of BioMonitor to detect episodes of AF was quantified in comparison to an external Holter ECG recorder (SpaceLabs Health Care, Lifecard CF). BioMonitor classifications and Holter episodes were directly compared to one another on an episode-by-episode basis.

BioMonitor correctly detected AF in all patients presenting with AF episodes during the Holter ECG. 63 out of 66 patients (95.5%) had analysable Holter data, 39/63 (62%) showed at least one true AF episode. All these patients had at least one AF episode stored in the ICM. On Holter monitoring, 24/63 (38%) patients did not show AF episodes, in 16 of them (16/24, 67%), the ICM confirmed the absence of AF. The AF detection sensitivity and positive predictive value for episodes' analysis were 95.4% and 76.3%, respectively.

5.2.3 BioMonitor 2 Pilot study[4]

The second generation ICM, BioMonitor 2, was first investigated in a feasibility study conducted in 31 patients in 5 Australian sites. The main objective of the study was to provide clinical data about the assessment of insertion procedure and the sensing quality of the device.

31 Patients were enrolled, of which one patient was excluded before insertion. Data of 30 patients from 5 Australian clinical sites from December 18, 2014 (first insertion procedure) to November 17, 2015 (end of last observation period) were analyzed.

The investigators had to evaluate the insertion procedure with the newly developed fast insertion tool (FIT) set. After the insertion and during the 1-week and 1-month follow-up visits sensing parameters were recorded.

All BioMonitor 2 insertions were performed successfully. The median insertion time was 2.5 min and the median of the total insertion time was 9.0 min. In most of the cases, handling of FIT 1 was assessed as `good´ by the implanter. Only in five patients additional force was required to form the pocket due to individual anatomy and tissue characteristics. The assessment of FIT 2 was given as `good´.

The mean R-wave amplitude at 1-week follow-up visit was 0.7 mV and demonstrated significant superiority to the R-wave amplitude of the predecessor BioMonitor with 0.3 mV (primary endpoint). BioMonitor 2 showed a remarkably lower noise burden of 1.3% (mean of all patients at 1-week follow-up) compared to the predecessor device BioMonitor of 5.5%.

Fourteen adverse events were reported until the end of the 1-month follow-up. Six patients suffered from pain in the pocket, but no medical action was needed and all events were resolved. One patient suffered from a wound infection after removing the sutures himself.

The results fulfil the expectations regarding the safety and efficacy of the BioMonitor 2 and its insertion tool set FIT1/2. The results have been published in an adequate scientific journal[63].

[2] Ciconte G. Atrial fibrillation detection using a novel three-vector cardiac implantable monitor: the atrial fibrillation detect study. Europace 2016.

[3] Clinical Investigation Report of the Single-center AF Detect study of the Implantable Cardiac Monitor BioMonitor, Version 1.0. 2015

[4] Clinical Investigation Report of the BIO|Master.BioMonitor 2 Pilot study of the Implantable Cardiac Monitor BioMonitor, Version 1.0. 2016

5.2.4 BIO|MASTER.BioMonitor 2 study[5]

The BIO|MASTER.BioMonitor 2 study (NCT02565238) was an investigation performed to provide clinical data on the BioMonitor 2.

The objective of the study was to confirm safety and efficacy of the BioMonitor 2 system, i.e. the BioMonitor 2 device and the fast insertion tools 1 and 2 (FIT1 and FIT2) set. The data were collected to support the regulatory approval of this product in countries outside the CE region. The clinical investigation is a post market clinical follow up (PMCF) study and carried out following the CE marking of BioMonitor 2. It was intended to answer specific questions relating to clinical safety or performance (i.e. residual risks) of the BioMonitor 2 system when used in accordance with its approved labelling.

The study was conducted as an open, prospective, multicenter, single arm, non-randomized international clinical trial. A total of 92 patients were enrolled (87 planned) among 13 sites in 4 countries. Patients were enrolled either in group 1 (no history of atrial fibrillation – AF -, 30 patients planned, 30 enrolled) or group 2 (current known and documented paroxysmal atrial fibrillation episodes or persistent atrial fibrillation either indicated for an ablation or already ablated within the four weeks before enrollment, 57 patients planned, 62 enrolled).

The enrollment started on September 28, 2015 and was completed on July 14, 2016. A total of 92 patients were enrolled. The last patient completed the study participation on October 25, 2016. 8.7 % of all enrolled patients exited the study prematurely.

The BioMonitor 2 was successfully inserted in 90 out of 92 patients who were enrolled. One patient withdrew consent before the BioMonitor 2 insertion procedure and in one case the insertion attempt failed due to a bent FIT 1. While the mean time between first skin cut and successful positioning of the BioMonitor 2 was 2.9 min, the whole mean insertion time was 7.4 min. The assessment of the FIT1 tool was good and acceptable in most cases. In 14.3% of the insertions additional force was required to tunnel and prepare the pocket and the insertion procedure was assessed as poor. The overall assessment of FIT 2 was evaluated as `good´ or `acceptable´ in 97.8%.

Fifty adverse events (AEs) were reported until the end of the 3-month follow-up. Two SADEs were reported in two patients with risk of erosion and subsequent explantation of the BioMonitor 2. The SADE-free rate was statistically significant higher than 90%. The primary endpoint was met.

The mean R-wave amplitude at the 1-week follow-up visit was 0.75 mV and demonstrated significant superiority to the R-wave amplitude of the predecessor BioMonitor (0.3 mV). Thus, the secondary endpoint was met. Moreover, the BioMonitor 2 showed a low and stable noise burden, which had a mean value of 3.0% and 3.4% at the 1-week and 3-month follow-up, respectively.

All endpoints were met. The study results confirm the safety and efficacy of the BioMonitor 2 system and show that the insertion procedure performance was overall rated between `good´ and `acceptable´ by the investigators[22,23]. A publication has been accepted[64].

[5] Clinical Investigation Report of the BIO|Master.BioMonitor 2 Study of the Implantable Cardiac Monitor BioMonitor, Version 1.0. 2017

Appendix to the Clinical Investigation Report[6]

An analysis report on arrhythmia detection performance was provided as an appendix to the Clinical Investigation Report of the BIO|MASTER.BioMonitor 2 study. The data consists of episode-recordings from the study device with concurrent 48 hour Holter ECG recordings, and was collected as additional data of interest in the study.

The performance of BioMonitor 2 in detecting episodes of atrial fibrillation, bradycardia, asystole, high ventricular rate and sudden rate drop was evaluated by an independent adjudicator by comparing device recordings with Holter ECG recordings. Characteristics of "binary classification" (PPV, NPV, sensitivity and specificity) were reported in episode based, patient averaged, patient based and duration based analysis. In 31 of 82 patients a total of 318 episodes of arrhythmia were detected.

BioMonitor 2 successfully identified all patients with arrhythmia (31 out of 31) and 99% (269 out of 272) of all true episodes of arrhythmia. Of all detections of the device, 85 % showed true arrhythmic episodes. The most frequent arrhythmia was atrial fibrillation (AF). Ninety-five of 98 AF-episodes were detected (sensitivity 97%). The positive predictive value was, depending on the analysis- approach, between 64% (patient-averaged analysis) and 93% (duration based analysis).

5.2.5 BioInsight[7]

The purpose of the BioInsight study (NCT02756338) was to evaluate the safety and feasibility of performing the BioMonitor 2 insertion procedure in an office setting. Data was collected from 77 subjects from insertion through 90-days of follow-up post-insertion.

Subjects were consented within 30 days prior to the insertion procedure and screened to ensure they met all of the inclusion and none of the exclusion criteria. Subjects with successful insertion procedures were required to complete an initial wound check visit 7 days (window -2, +7 days) after the procedure and a routine follow-up visit at 90 days (window -15, +30 days) post-insertion. The rate of insertion procedure-related adverse events (AEs) within 90 days post-insertion that required additional invasive intervention to resolve was assessed. Data was also collected on the safety and feasibility of in-office insertion procedures. No prespecified hypotheses were tested in this study.

Two adverse events were reported during the study. Both were classified by the Clinical Events Committee as insertion procedure-related not requiring invasive intervention and therefore did not meet the criteria for a primary objective. The primary result was thus 0% (95% CI: 0.0%, 5.0%). Hence both events contributed to the secondary objective (all insertion procedure – related events) resulting in an overall event rate of 2.7 % in 73 patients (95% CI: 0.3%, 9.5%).

5.2.6 BIO|CONCEPT.BIOMONITOR III study

The BIO|CONCEPT.BIOMONITOR III (NCT03850327) is a First-in-Man study which started in March 2019. The objective is to confirm the safety and performance of the BIOMONITOR III system. Furthermore, the insertion procedure, the use and handling of the incision and insertion tools and the sensing quality of the BIOMONITOR III will be investigated. For this purpose 45 patients have been enrolled at 10 Australian sites. All patients have been inserted with a a BIOMONITOR III and have been followed until 1 month after insertion. The Last Patient Out was in June 2019. All data are expected to be entered and monitored until July 2019. A final Clinical Investigation Report is expected in September 2019.

[6] Analysis Report for the Arrhythmia Detection Performance of the BIO|MASTER.BioMonitor 2 Study, Version 1.0, 2017

[7] Final Report of the BioMonitor 2 In-Office Setting Insertion Safety and Feasibility Evaluation With Device Functionality Assessment (BioInsight), 2017

5.2.7 BIO| STREAM.ICM registry

In parallel to the BIO|MASTER.BIOMONITOR III study, the BIO|STREAM.ICM will start about the same time as the Master Study. This investigation is designed to provide long-term clinical data of outcome, efficacy and residual safety aspects of BIOMONITOR III in an unselected, real-life clinical set-up. Given its character as a registry study, a fixed follow-up schedule, predefined endpoints or additional restrictive inclusion criteria are not applicable.

5.3 Justification

The main objectives of this study are to confirm safety and performance of the BIOMONITOR III system. The aim of the study is to identify and evaluate residual risks associated with the use of the BIOMONITOR III system that are discovered or remain even after risk analysis, risk mitigation and successful conformity assessment.

Clinical studies of the predecessor have shown that the concept of the implantable cardiac monitor is safe and efficient (see section 0). Prior to this Master Study the new insertion procedure of BIOMONITOR III was extensively tested in bench tests and in a cadaver and animal study as well as in a First-In-Man study (see above). The BIOMONITOR-III received the CE mark in June 2019.

In order to provide further supporting clinical evidence with regard to the BIOMONITOR III safety and performance, and to identify possible residual risks, one primary endpoint to assess the device safty and four secondary endpoints to assess device efficacy were defined (see also section 7.2).

As **primary endpoint** the SADE-free rate was chosen because the main difference of the BIOMONITOR III compared to its precursor is reduced size and novel incision and insertion tools, which creates a residual risk that device or procedure-related adverse events of unexpected nature or frequency occur. Such events would be observed during the insertion procedure or post-insertion. As the majority of the ICM complications are usually found in the early postoperative period, a follow-up duration of 3 months is deemed to be sufficient for this endpoint. The majority of the ICM complications are usually found in the early postoperative period. However, in order to cover the whole spectrum of adverse events an extended follow-up period of 3-months was chosen to cover also long-term events such as e.g. infections. The threshold for the respective hypothesis is set to 90% SADE-free rate, on the basis that this is a value that:

- allows for comparison with preceding studies (e.g. BIO|MASTER.BioMonitor 2, where the SADE-free rate threshold was also set to 90%), and
- is a standard expected and approved by European and international regulatory authorities.

It will also be checked, in all follow-up consultations, whether further Adverse Events (AEs) and Device Deficiencies (DDs) occurred at the time of or after insertion.

Secondary endpoint 1 and 2 for the BIOMONITOR III evaluate the efficacy of the ICM's appropriate sensing. Compared to predecessor devices, the changes in size and tip might change the characteristics of the electrical contact of and the electrical potential between the poles. It is expected that the R-wave amplitude will be slightly reduced because of a shorter distance between the sensing electrodes. Therefore the R-wave amplitude and noise burden will be assessed.

Secondary endpoint 3 evaluates the P-wave visibility as assessed by the investigator. P-wave detection helps to support the identification of correctly detected and classified episodes. For physicians, the presence or absence of the P-wave and its distance from the R-wave on an ECG is very important information for the interpretation of an ECG. The assessment is based on the evaluation of the ability of a physician to recognize P-waves in the stored sECGs of the BIOMONITOR III as a diagnostic criterion.

Secondary endpoint 4 evaluates the SADE-free rate related to the BIOMONITOR III 12 months after insertion to confirm the safety of the BIOMONITOR III system from insertion until

the 12-month follow-up. Due to suggestions of the notified body to cover a large proportion of the life-time of the devices, the follow-up duration for the study was extended to 12 months as compared to 3 months. However, the study duration does not cover the entire life-time of the devices and therefore, additional measures will be taken to comply with the active PMCF requirements for e.g. Post-Market Surveillance activities.

Further data of interest are collected to assess arrhythmia detection and the insertion procedure of the BIOMONITOR III (see section 7.5).

Data from insertions and follow-ups are recorded in eCRFs, supplemented by clinical and device data collected through Home Monitoring. Home Monitoring allows for the reliable and continuous collection of many parameters directly as source data. By combining the Home Monitoring data with the clinical data from eCRFs, comprehensive information on BIOMONITOR III is available for analysis.

The primary purpose of the device is arrhythmia detection; however the arrhythmia detection algorithms remain unchanged between BioMonitor 2 and BIOMONITOR III. BioMonitor 2 performance in this respect has already been established in the BIO|MASTER.BioMonitor 2 - Arrhythmia detection performance analysis (see section 5.2.4). Because of the shorter device dimension and sensing vector it is assumed that R-wave amplitudes will be smaller in BIOMONITOR III. It cannot be excluded that this may have an effect on the detection performance. Therefore, the arrhythmia detection performance of BIOMONITOR III will be analyzed as additional data of interest.

As the BIOMONITOR III system will be used for the first time in clinical routine a significant number of patients (up to 157 patients) and about 30 experienced investigators shall be included in this Master Study. Sample size calculation is based on safety and performance endpoints. It will be shown that 3-month follow-up is considered sufficient to evaluate the safety of the BIOMONITOR III. Performance of the BIOMONITOR III will be demonstrated by assessment of the appropriate QRS detection which is the base of all automatic arrhythmia detection. This will be established with comparison between the sECG of the BIOMONITOR III and the ECG of Holter ECG devices. Long-term data will be collected until 1 year after insertion. Furthermore, the safety through 12 months will be evaluated.

The BIO|MASTER.BIOMONITOR III study is designed as an international and multi-center study. The number of sites and the maximum number of patients per site will be chosen to ensure the multicentric character of this study, i.e. a reduction of investigator- or site-related bias. Therefore, the design of this clinical investigation is considered adequate to collect and evaluate post-market data to identify and evaluate residual risks associated with the use of the BIOMONITOR III, which are discovered or remain even after risk analysis, risk mitigation and successful conformity assessment. There are no formal subgroups in which the endpoint analysis would be done separately. Furthermore, the in- and exclusion criteria are defined in a way to allow for the enrollment for an unselected, representative patient collective at the sites.

Despite the proven safety level of approved devices and a generally accepted risk-benefit profile of ICM technology, the identification and mitigation of residual risks by means of post-market clinical follow-up of medical devices is permanent obligation, as required by notified bodies, regulatory authorities and guidelines. Obtaining safety data outside of clinical trials may underestimate the incidence rate of AEs and provide only little information on the potential reasons for the events[34,35]. Due to its design, this Master Study is expected in particular to provide data on AEs and their medical context, helping to identify residual risks regarding device safety.

6 RISKS AND BENEFITS OF THE DEVICE AND CLINICAL INVESTIGATION

6.1 Anticipated clinical benefits

By participating in this study, patients receive a modern device with many potential clinical benefits. In addition, they will benefit from being intensively surveilled by Home Monitoring throughout the course of the study.

The benefit of utilising of ICMs in the management of syncope has been proven in many studies (e.g. EaSyAS[65], ISSUE-2[66]). With ICMs, diagnostic yield is improved compared to conventional testing[67–69,69–71]. This improved diagnostic accuracy translates into the delivery of more specific therapy[27,28,72,73]. There is data to suggest that syncope burden can be reduced based on an early ICM based therapeutic decision[27,67,72,74]. In addition, ICMs aid in establishing the diagnosis of AF[41,44,75]. The use of ICMs for continuous cardiac rhythm monitoring has been shown to be superior to other means of ECG monitoring for AF screening in ischemic stroke patients[76]. ICMs have also been successfully utilized in the assessment of various AF ablation therapies[36,44,77]. The ultimate goal of AF monitoring will be to guide the clinical management of AF patients[29,34,56]. For a patient with suspected AF who requires extensive monitoring of cardiac rhythm, the overall benefits provided by an ICM are greater than the limited disadvantages of over- or under-detection of AF.

Incorrect detections remain a significant problem amongst the current generation of ICMs. The large sensing vector of BIOMONITOR III is expected to yield a large QRS amplitude detected and reduce the degree of noise. This is expected to lead to a reduction in misdiagnoses and the improved performance of BIOMONITOR III´s auto detection features.

Patients are expected to benefit from the ICM insertion and the long-term monitoring of clinical parameters using Home Monitoring. However, a direct benefit from participating in the Master Study is not expected for the patients due to the the fact that the treatment follows routine. The main benefit for the patients is indirect and results from collecting data on long-term device safety and the device therapy, which will help to improve future devices generations and in turn, increase patient safety and efficacy of the therapy.

6.2 Anticipated risks

6.2.1 Anticipated adverse device effects

Adverse device effects (ADE) anticipated for patients with ICM insertions are described in section 18.7 of this clinical investigation plan. Since no additional device related procedures outside the clinical routine care are required during participation in BIO|MASTER.BIOMONITOR III, no further study-specific ADEs are anticipated.

Complications for patients and device systems generally recognized among practitioners also apply to BIOTRONIK devices. Primary sources of complication information include current scientific and technological knowledge. Complications may include, but are not limited to, device rejection phenomena (including local tissue reaction), fluid accumulation within the device pocket, hematoma, infection, migration of the device and erosion through the skin.

6.2.2 Residual risks associated with the device

In principle, technical failures in any implant due to component failures, or other events that could compromise functioning, cannot be completely ruled out; they occur, however, very rarely. Instructions for use inform the users about hazardous usage conditions, but user errors cannot be prevented completely. There may be other risks associated with the devices that are currently unforeseeable.

6.2.3 Risk associated with participation in the study

Only patients will be enrolled, which are foreseen by the investigator for an ICM insertion. The procedures of the study follow cardiological routine treatment and can be considered to be of very low risk.

There are no known medical risks for the patient when using the Home Monitoring platform. Data protection may be compromised if an inadequate patient ID is used for registration of the patient by the physician in the HMSC.

Unauthorized access to the patient data or inadequate data protection (e.g. submission of non-pseudonymized data to the sponsor representatives) are possible risks associated with the participation. BIOTRONIK undertakes technical and organizational measures to protect patient's data privacy and adheres to applicable European data protection laws.

Insertion of BIOMONITOR III does not differ significantly from the procedures applicable for comparable systems. Thus, no additional risks or burdens concerning device insertion derive from participation in the study.

6.2.4 Possible interactions with concomitant medical treatments

For the insertion of the BIOMONITOR III, no interactions with concomitant medication or other medical treatment are expected.

The individual cardiovascular medication may have to be adapted to the patient's needs independent of the BIOMONITOR III.

6.3 Steps to control or mitigate the risks

Risks associated with BIOMONITOR III which are mentioned above, as well as in section 18.7 have been reduced by special risk mitigation measures listed in the risk analysis of BIOTRONIK.

They are minimized through the utilization of strict aseptic technique, compliance with the technical manual, compliance with this clinical investigation plan and technical procedures, adhering to the guidelines for selection of patients, close monitoring of the patient's physiologic status during the procedures, and by promptly supplying BIOTRONIK with all pertinent information required by this clinical investigation plan.

Remote surveillance of the patient may be impaired as the timely receipt of Home Monitoring notifications and trend messages cannot be guaranteed; therefore the physician will be notified in case several expected trend messages from certain devices are missing.

Data protections laws, in particular European Community Directive 95/46/EC and its respective national versions must be followed where applicable. Thus, patient names may not be used as patient IDs within the HMSC. Non-pseudonymized data inadvertently sent to the sponsor will be handled upon discovery according to BIOTRONIK's internal processes to ensure that only pseudonymized documents are available at and used by the sponsor. Access to the HMSC and the clinical data management system (CDMS) is restricted by secured internet platforms using user IDs and passwords. Further details on the risk mitigation regarding the CDMS are outlined in the data management plan of the Master Study. Nevertheless, a residual risk remains.

6.4 Risk-to-benefit rationale

Patients participating in this Master Study have an indication for an ICM and receive an ICM independent of their Master Study participation. Also the Home Monitoring might be used routinely. The BIOMONITOR III and the Home Monitoring platform are used within their intended purpose and are market approved in their respective countries, with exception of Australian sites (see section 4.3).

The benefit of the use of ICMs has been proven in different studies. It is important to point out that the physician will always have to weigh the benefits against rarely occurring complications

on a case-by-case basis. In this case, the general risk/benefit analysis shows that the benefits for the patient clearly outweigh the risks.

Patients will benefit from the most advanced BIOTRONIK ICM technology. Patient monitoring mandated by the clinical investigation plan in the form of follow-ups and continuous observation via Home Monitoring ensures optimal patient care.

By participating in this study, patients contribute to medical progress which may benefit other patients in the future.

Possible risks are associated with the general use of ICM systems and are not related to the study procedures.

Therefore it is concluded that the benefits of the BIO|MASTER.BIOMONITOR III study outweigh the risks.

7 OBJECTIVES AND HYPOTHESES

7.1 Objectives

This study is designed as a post-market clinical follow-up study to identify and evaluate residual risks associated with the use of the BIOMONITOR III system that are discovered or remain even after risk analysis, risk mitigation and successful conformity assessment. The results will be used to update the clinical evaluation. Furthermore, the study will also provide additional data as required by regulatory authorities outside of the CE-region.

The functionality of the BIOMONITOR III is very similar to its predecessor BioMonitor 2, thus, new functionality is not in the main focus of this study. The focus of this study is primarily on the safety of the BIOMONITOR III system including the insertion procedure.

7.1.1 Primary objective

The primary objective of this study is to confirm safety of the BIOMONITOR III system by recording and evaluating all Serious Adverse Device Effects (SADEs) related to the BIOMONITOR III, the Incision and FIT OneStep Insertion Tool and the insertion procedure until 3 months.

7.1.2 Secondary objectives

Secondary objectives are to verify the sensing performance of the device by evaluating the R-wave sensing amplitude, noise burden and P-wave visibility. Another secondary objective is long-term safety over 12 months.

7.2 Endpoints and hypotheses

7.2.1 Primary endpoint and hypothesis

SADE-free rate until the 3-month follow-up

A primary endpoint is an SADE (see definition in section 18) that is possibly, probably or causally related to the BIOMONITOR III, the Incision Tool or the Insertion Tool, or the insertion procedure, which occurs before the 3-month follow-up.

SADEs will be adjudicated by an internal adjudication board, whereby the seriousness and device relatedness will be re-examined. If any amply documented external physical influence (e.g. accident, sport) or medical AE caused the SADE, it does not contribute to this endpoint. SADEs that occur later than the 3-month follow-up, and SADEs with onset date later than 105 days after insertion procedure (3 months defined as 91 days after implantation + 14 days would still be in accordance to the CIP) in case the 3-month follow-up was not conducted or conducted outside the specified time interval, do not contribute to this endpoint.

The parameter of interest p_{SADE} is the SADE free rate, which will be calculated by

$$1 - \frac{\text{Number of patients with one or more primary endpoint until the 3 months FU}}{\text{Number of patients at the 3 months FU or with primary endpoint}}$$

in percent. The period of observation starts with the insertion of the BIOMONITOR III and takes until the 3-month follow-up.

It is expected, that the SADE-free rate will be significantly above 90%. Therefore the corresponding hypotheses definitions are:

Null hypothesis: $H_0: \quad p_{SADE} \leq 90\%$

Alternative hypothesis: $H_A: \quad p_{SADE} > 90\%$

The following patients are not included in the analysis set for this endpoint:

- Patients without SADE, prematurely terminated before the time window for the 3-month follow-up, i.e. less than 77 days after insertion procedure (3 months defined as 91 days after implantation – 14 days would still be in accordance to the CIP).

7.2.2 Secondary endpoints

The following 4 secondary endpoints are defined for the study.

R-wave amplitude

The **secondary endpoint 1** evaluates the R-wave amplitude at the 1st follow-up and at 3-month follow-up by measuring both, the lowest and the highest amplitude value via the programmer.

Noise burden

The **secondary endpoint 2** evaluates the noise burden at the 1st follow-up and at 3-month follow-up by retrieving the percentage of noise via the programmer.

Assessment of P-wave visibility

The **secondary endpoint 3** evaluates the P-wave visibility at 1st, 3- and 12-month follow-up. The investigator will evaluate whether P-waves can be recognized in the stored sECGs showing sinus rhythm. The number of heart cycles and observed P-waves which can undoubtly be identified in ECGs will be assessed by the investigator.

SADE-free rate until the 12-month follow-up

The **secondary endpoint 4** is the SADE-free rate related to the BIOMONITOR III 12 months after insertion.

7.3 Claims and intended performance

Recent changes in legislature require that any statements made for the promotion of medical products must be based on scientific evidence. These statements are called `promotional claims´.

In this clinical investigation the following promotional claims shall be supported:

Table 2: List of promotional claims related device features and study endpoint.

Promotional Claim	Feature	Related endpoints / data of interest
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Promotional Claim	Feature	Related endpoints / data of interest
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Promotional Claim	Feature	Related endpoints / data of interest
- [redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

7.4 Safety assessments

The primary endpoint addresses the safety of the study device. Further, all adverse events will be recorded and summarized (see section 18). These events will be assessed as defined in the SOPs of the sponsor.

7.5 Further data of interest

Beyond the objectives defined in section 7.1, the study is designed to collect further data of interest. The data on the following topics will be considered `data of interest´ and may be analyzed, as appropriate:

- Demographics
- Medical history
- Indication for ICM
- Usage of incision tool and assessment of incision tool handling
- Assessment of insertion procedure: performance of insertion tool and ease of use (e.g. insertion time, handling and positioning)
- Insertion site
- Insertion success rate
- Wound closure
- Positioning of BIOMONITOR III
- Comfort after wound healing
- Explantation data of BIOMONITOR III
- Additional implantation of BIOMONITOR III
- Serial number of used study devices

- Performance of arrhythmia detection (will be assessed by comparing the BIOMONITOR III detected arrhythmia episodes recorded against a 48-hour Holter ECG, if applicable)
- Syncope and AF: detailed analysis of sensing performance in device-triggered ECG-episodes
- AF burden
- Assessment of device programming: individualized programming and re-programming of the device
- Assessment of programmer and programmer software performance
- Remote Assistant III trigger success rate after insertion procedure
- Home Monitoring Data (e.g. transmission success)
- HM workflow efficiency
- Assessment of BIOMONITOR III repositioning (if applicable)
- Assessment of BIOMONITOR III migration (if applicable)
- Usability of Patient App (if applicable)
- Information on application of imaging techniques, if applicable (e.g. MRI, mammography)
- Diagnosis and further treatment
- Adverse events and device deficiencies

8 DESIGN OF THE CLINICAL INVESTIGATION

8.1 General considerations

8.1.1 Type of clinical investigation

The BIO|MASTER.BIOMONITOR III is designed as an open, prospective, single arm, non-randomized international study.

8.1.2 Measures taken to minimize or avoid bias

No randomization or blinding of the investigator is necessary in this study, because the study does not require a control group. The clinical investigation is designed and will be conducted, analyzed, and reported based on an internal Standard Operating Procedure (SOP) system to minimize and avoid any bias.

It is planned to conduct this study in approximately 30 international sites with several physicians per site. Thereby an adequate level of heterogeneity of countries, sites and investigators is ensured to obtain representative results.

To minimize bias from very high recruitment rates of single sites, a limitation of the maximum number of patients per site is defined for the study. To minimize site-specific bias, the maximum number of patients per center will be n=30.

8.1.3 Selection of measurements for endpoints

For the primary endpoint, the SADE-free rate will be assessed by collecting and evaluating adverse events until the 3-month follow-up (see section 7.2.1).

For **secondary endpoint 1**, the R-wave is measured via the programmer. Due to its automatic measurement, this figure unambiguously indicates the device's ability to detect the patient's heart beats. The noise burden for **secondary endpoint 2** is continuously recorded by the device. The value retrieved from the device with the help of the programmer clearly measures the time during which the device is unable to detect the patient's heartbeats.

P-waves are not detected by the device; therefore, the investigators decide whether P-waves are visible in a test ECG. A periodic sECG was chosen as the sample ECG because during arrhythmia, P-waves are often not present. The P-wave visibility (**secondary endpoint 3**) is determined by counting P-waves and QRS-complexes.

For the **secondary endpoint 4** the long-term safety of the BIOMONITOR III system, all SADEs related to the BIOMONITOR III system are collected by the investigators and evaluated by an internal adjudication board as described above. An observation period of 12 months was chosen to significantly extent the monitoring period for safety events beyond the 3 months which are defined for the primary endpoint.

8.1.4 Methods

8.1.4.1 eCRFs

During the course of the study, all clinical procedures are performed according to clinical routine. All parameters and measurements that are recorded within the study are described in this section and are documented on the following electronic Case Report Forms (eCRFs). The corresponding time schedule is described in section 9.1:

- Enrollment
- Baseline
- Medical History
- Insertion

- 1st follow-up
- 3-month follow-up
- 12-month follow-up
- Adverse Event
- Device Deficiency
- Device Log
- Explantation/Deactivation
- Concomitant Medication Log
- Deviation Log (site)
- Device Accountability Details (for Australia only)
- Termination

Source data, e.g. medical records, have to be available for all data entered in the eCRFs, unless specified differently by this CIP (compare sections below). eCRFs will be verified by the sponsor's clinical monitors.

If necessary, the sponsor will request pseudonymized electronic source documents (e.g. exported programmer files or medical records about AEs for the assessment of seriousness and relatedness).

Patients have to consent to the use of their medical data prior to enrollment by signing the informed consent form (ICF).

8.1.4.2 Source data verification of enrollment criteria

For the following inclusion/exclusion criteria, the eCRF is accepted as source:

- Patient is able to understand the nature of the study and to privide written informed consent.
- Patient is willing and able to perform all follow-up visits at the investigational site.
- Patient is pregnant or breast feeding.
- Patient is participating in another interventional clinical investigation.
- Patient´s life-expectancy is less than 12 months.

The following Source data sheets (SDS) are recommended to be used:

- Insertion SDS
- 1st follow-up, 3-month and 12-month follow-up SDS
- Explantation / Deactivation SDS

8.1.5 Equipment to be used for the assessment of variables

The following equipment is used during the study to collect data in combination with the BIOMONITOR III or as accessory:

- External programming device: BIOTRONIK Renamic (or successors)
  BIOTRONIK ICS3000 (or successors)
- BIOTRONIK programmer software: Programmer software PSW1901.A/1 (or successor versions)
- Remote monitoring tools: CardioMessenger II

CardioMessenger II-S

BIOTRONIK Smart 3G (or successors)

BIOTRONIK Smart 3G AU (or successors)

- Remote monitoring software: HMSC 3 or successors
- Holter ECG: Pathfinder®, Spacelabs Heartcare
- Clinical Data Warehouse (platform for acquisition of study-related pseudonymized Home Monitoring data)

All devices are used within their intended purpose.

8.1.6 Replacement of subjects

A drop-out rate of 10 % of the total sample size was taken into consideration based on estimates taken from experiences with predecessor devices.

During the course of the study, patients who drop-out prior to any insertion attempt will not be counted in the total sample and will be replaced as long as study enrollment is ongoing.

8.2 Used devices and comparators

8.2.1 Description of exposure to the investigational device

The BIOMONITOR is an Active Implantable Medical Device (AIMD). According to the nature of implantable devices, the investigational device used in this study will be inserted into the patient´s body. It may remain in the patients' body until either a diagnosis has been established for the medical issue for which it has been implanted, or until its battery has reached the end of its service time. Even then, it is in the responsibility of the patient and the responsible physician to decide if the device is explanted or remains in the patient's body.

8.2.2 Justification of the choice of comparators

No comparator is used in this study.

8.2.3 List of any other medical device and/or medication to be used during the investigation

Other medical devices used within this study are listed in section 4.3. Further, an external 48-hour holter recorder will be applied. During conduct of the insertion procedure, anesthesia may be used. Additionally, local or systemic antibiotics may be applied to prevent wound infection according to local clinical practice.

No medication is required by this study protocol. However, the medication is at the investigator's discretion according to the medical condition of the patient.

8.2.4 Number of investigational devices to be used and a justification

One BIOMONITOR III per study patient will be used. Additional investigational devices may be used due to device exchange during the study, but this appears unlikely since the nominal lifetime of the device exceeds the study duration.

8.3 Subjects

8.3.1 Description of patient population

Only patients with an indication for ICM system insertion according to current clinical practice and who are planned to be inserted with a BIOMONITOR III according to the investigators` decision may be enrolled in the BIO|MASTER.BIOMONITOR III study. Decision for insertion of the respective BIOTRONIK devices should be based on medical decisions alone and should not

be influenced by the enrollment to this clinical trial. The patient population consists of patients in whom long-term cardiac rhythm monitoring is required for diagnostic purposes. Indications are described in sections 4.1.3 and 4.6.1.

8.3.2 Inclusion criteria

To be eligible for participation in the BIO|MASTER.BIOMONITOR III study, patients must fulfill the following inclusion criteria:

- Patient is at high risk of developing a clinically important cardiac arrhythmia; **or**

  Patient is undergoing investigation for symptoms such as palpitations, pre-syncope or syncope, that are suggestive of an underlying cardiac arrhythmia; **or**

  Patient is undergoing investigation for the detection of atrial fibrillation following cryptogenic stroke; **or**

  Patient is planned for AF ablative procedure or has already undergone an AF ablative procedure.
- Patient is able to understand the nature of the study and to provide written informed consent.
- Patient is willing and able to perform all follow-up visits at the investigation site.
- Patient is willing and able to use the CardioMessenger and accepts the BIOTRONIK Home Monitoring® concept.

8.3.3 Exclusion criteria

The following exclusion criteria shall **not** be fulfilled for enrollment of the patient:

- Patient is implanted with an ICD or pacemaker.
- Patient is pregnant or breast-feeding. Patient is less than 18 years old.
- Patient´s life-expectancy is less than 12 months.
- Patient is participating in another interventional clinical investigation according to the definition given below.[8,9]

Note: The inclusion and exclusion criteria apply at enrollment.

8.3.4 Screening failure

No screening procedure is planned for this study.

8.3.5 Drop-out criteria

Since no invasive, stressful or risky procedures are planned by this protocol after the insertion, it is not allowed that a patient is excluded from the study by decision of the investigator once

[8] Based on the EU Clinical Trials Regulation a study is considered as interventional which fulfils any of the following conditions: (a) the assignment of the subject to a particular therapeutic strategy is decided in advance and does not fall within normal clinical practice of the Member State concerned; (b) the decision to prescribe the investigational medicinal products is taken together with the decision to include the subject in the clinical study; or (c) diagnostic or monitoring procedures in addition to normal clinical practice are applied to the subjects.

[9] [redacted]

an insertion has been attempted. This does not infringe on the investigators' right, and obligation, to refrain from any study procedure that may not be medically justified. It is merely intended to assure complete reporting of adverse events from the complete study duration.

A drop-out is possible as described in 8.3.5.1 to 8.3.5.6.

8.3.5.1 Patient unable or unwilling to attend required visits

The patient should be prematurely terminated if he or she is permanently unable or unwilling to attend required follow-ups, e.g. if they move away from the investigational site, if they are permanently bed-ridden and have no appropriate transport option, or in comparable cases.

8.3.5.2 Patient is lost to follow-up

The patient should be permanently terminated if he or she is permanently lost to follow-up. In such a case the investigators shall use all justified means to try and contact the patient before premature termination.

8.3.5.3 Patient withdraws consent to study participation

Patients may withdraw their consent for study participation at any time without stating the reason and without any unfavorable consequences. All data which are collected 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 then. A withdrawal sheet and a study termination CRF have to be filled in by the investigator.

8.3.5.4 Drop-out according to protocol

The investigator shall exclude a patient due to the following reasons and after all adverse events have been reported and the corresponding eCRFs have been thoroughly completed:

- Patient with no insertion attempt of the BIOMONITOR III within 4 weeks of enrollment
- Patients in whom the insertion fails and no new attempt is planned are terminated after complete reporting of the insertion attempt and all adverse events connected to the failed insertion.
- Patients in whom the BIOMONITOR III was replaced/explanted/deactivated are terminated after complete reporting of the explantation and all adverse events connected to the explantation.

8.3.5.5 Patient death

The investigator shall terminate the patient's study participation after their deaths and report the death as an adverse event on the corresponding eCRF.

8.3.5.6 Enrollment failure

The patients' study participation shall be terminated if, prior to any medical procedure that is required by the study protocol, it is discovered that the patient violates an inclusion criterion or fulfills an exclusion criterion.

8.3.6 Point of enrollment and study termination

The date of enrollment is the date of of the informed consent form. Study related procedures, documentation and collection/following of adverse events will start from this time on.

The point of study termination is defined as date of 12-month follow-up for patients with regular study termination.

In case of premature study termination the following rules apply:

- If patients are permanently unable to attend required follow-ups, e.g. if they move away from the investigational site the date of study termination should be the date of last contact of the study team (e.g. investigator or study nurse) with the patient.
- If patient is lost to follow-up, the date of termination shall be the last day, from which the investigator can assume that possible adverse events – had any occurred – would have been reported. In most cases, this would be the date of the last follow-up contact.
- In case of withdrawal of a patient's consent, the date of study termination should be the date of withdrawal of consent.
- If the investigational device could not successfully be inserted, the date of study termination should be the date of the last unsuccessful insertion attempt.
- If the BIOMONITOR III is replaced/explanted/deactivated (e.g. due to subsequent therapies with pacemaker or ICD etc.), the date of termination is the date of explantation.
- In case of patient death, the date of study termination should be the date of death.
- In case the patient terminated prior to study specific procedures because a violation of an inclusion/exclusion criterion was discovered the date when the violation was discovered shall be the date of termination.

Study related procedures and documentation should end at the day of study termination for the respective patient. However, all Serious Adverse Device Effects will be followed for up to 4 weeks after study termination of the respective patient.

8.3.7 Timelines

First patient in (FPI)*:	~ Sep 2019
Last patient in (LPI)*:	~ May 2020
Enrollment period:	~ 9 months
Last patient out (LPO)*:	~ May 2021
Duration of study participation:	~ 12 months
Finalization of study report	~ Aug 2021

The end of the clinical study is defined as the date of study termination of the last patient (Last Patient Out).

* Timelines subject to change without requiring protocol amendments.

9 STUDY PROCEDURES

9.1 Overview

The following study related procedures (Table 3) apply and have to be documented in the respective electronic case report form (eCRF) for each patient enrolled. Subsequent to the enrollment and the insertion of the investigational device, three follow-up visits are scheduled - 1st follow-up after 10 days to 4 weeks after insertion, after 3 months and 12 months after insertion (± 14 days). A 48-hour Holter ECG is applied during the 1st follow-up procedure (10 days to 4 weeks after insertion at the latest).

The visits need to take place within a certain time frame as listed in Table 3. However, if circumstances prevent a protocol conform timing of the follow-up, the follow-up shall be performed anyhow and the reason for the protocol violation has to be indicated on a CIP deviation form. If circumstances prevent the presence of the patient at the follow-up visit, the reason for the missed follow-up has to be indicated on the eCRF.

Table 3: Overview of study procedures.

Investigations	Enrollment/Baseline	Insertion	1st follow-up (10 days to 4 weeks after insertion)	48-hour Holter- ECG	Month 3 (± 14 days)	Month 12 (±14 days)
Patient informed consent	x					
Verification of in- and exclusion criteria	x					
Demographics and medical history	x					
Indication for ICM	x					
Medication log	x	x[1]	x[1]		x[1]	x[1]
Insertion of BIOMONITOR III: Information on procedure and assessment of insertion procedure and tool handling		x				
Check of insertion location (wound check)			x		x	
Rating of wearing comfort (after wound healing)			x		x	
Migration of BIOMONITOR III			(x)		(x)	(x)
Explantation of BIOMONITOR III			(x)		(x)	(x)
R-wave measurements (highest and lowest value amplitude)		x	x		x	x
P-wave visibility assessment			x		x	x
Noise burden (%)			x		x	x
Program settings (ProgramConsult and SensingConsult)			x		x	x
Usage of indication-based program sets		x	x		x	x
Program periodic subcutaneous ECG (cycle duration 1 day `daily´)		x				
Program periodic subcutaneous ECG (cycle duration 30 days `periodic´)			x			
Changes in device programming			(x)		(x)	(x)
Device interrogation and electronic data file up-load via ReportShare		x	x		x	x
Apply Holter ECG and read out Holter ECG recordings after 48 hours				x		

Provide CardioMessenger (mendatory) and Remote Assistant III (otional, incl. test of Remote Assisstant III)		x				
Activation of Mome Monitoring and registration at the Monitoring Service Center		x				
Usability of Patient App			(x)		(x)	(x)
Documentation on application of imaging techniques (MRI, mammography)			(x)		(x)	(x)
Assessment of programmer performance and programmer software		x	x		x	x
Regular study termination						(x)
Adverse Event and Device Deficiency reporting	x	x	x	x	x	x
Fill-in eCRFs	x	x	x		x	x

(x)=if applicable

[1]In case of an Adverse event

The above mentioned procedures have to be documented in the eCRFs if they are conducted (Table 3). The use of Source Data Sheets is recommended.

9.2 Enrollment and baseline evaluation

Prior to enrollment into the clinical investigation, the investigator has to check whether all inclusion criteria are met and the absence of all exclusion criteria is confirmed. For the enrollment to be valid, the informed consent form has to be signed and dated both by the patient and the investigator. The date of enrollment is defined as the date the patient signed the informed consent. The informed consent process has to be documented in the patient record. After obtaining informed consent, the subject has to be registered in the iMedNet System. After registration, the patient will be assigned a ID code to be used in the study and the patient has to be entered in the patient identification log. The signed informed consent will be verified by sponsor appointed monitoring personnel.

On the enrollment eCRF the following data have to be recorded:

- Version number of the ICF
- Confirmation that the patient met all inclusion and none of the exclusion criteria
- Date of patient signature on the informed consent form
- Date of investigator signature on the informed consent form

After a subject has been enrolled, the following data have to be collected and entered in the Baseline – General, Medical History, and Concomitant Medication Log eCRF, respectively:

- Date of baseline assessment
- Demographic data
- Details on the ICM indication of the patient
- Medical history
- Current concomitant medication

Note: Medication shall be documented in the medication log at baseline and in the context of Adverse events.

9.3 Insertion

The device insertion shall be completed within 4 weeks after informed consent. Otherwise the patient is prematurely excluded from the study and a Termination eCRF has to be filled in. The insertion of the BIOMONITOR III is performed as described in the function manual and in section 4.7.1.10.

The implanting physician determines and documents the device position in accordance with the individual patient characteristics.

During insertion, the handling of the incision and insertion tools will be assessed by the implanting physician. The physician rates the performance as 'excellent', 'good', 'fair', 'poor' or 'very poor' . Furthermore the number of device repositioning has to be documented.

9.3.1 Procedure after device insertion

The following procedures shall be conducted after insertion:

- Interrogate the newly inserted BIOMONITOR III.
- Perform R-wave measurements (see section 9.5.1).
- Program the BIOMONITOR III according to the clinical indication of the patient.
- Use the indication specific program settings (Go to 'Parameters' – 'Program sets' – 'ProgramConsult', Figure 9) if possible.

Figure 9: Use **'**ProgramConsult**'** for indication specific programming.

- **Note:** It is strongly recommended that the high pass signal filter is keept at standard value 0.5 Hz.
- Check that the Home Monitoring function is set to 'ON'.
- Store the electronic procedure data (including final device settings, measurements) of the BIOTRONIK programmer. Provide the programmer data by uploading the PDF-File via the ReportShare-function (see 4.7.1.11 and 9.5.4).
- **Note:** Provide CardioMessenger to the patient and register the patient at the Home Monitoring Service Center (HMSC).
- Activate a periodic sECG recording in the 'Patient profile' tab of the HMSC (Go to 'Remote scheduling', press 'edit' and select 'daily'), Figure 10.

Figure 10: Activate daily periodic sECG recording in HMSC.

- Explain to the patient how to use the Remote Assistant III correctly and test the functionality of the Remote Assistant III. Let the patient trigger one sECG recording. If the first attempt was not successful, try to find the reason and try again. Check then if an sECG has been finally stored and report on the eCRF.
- If applicable, provide the Remote Assistant III to the patient for further follow-up.
- Answer questions regarding programmer and programmer software handling and document possible problems[10] regarding device programming.
- Enter data in the insertion eCRFs in the iMedNet EDC database. The use of source data sheet is recommended.
- Document any adverse event or device deficiency during the procedure by using the respective eCRF. Please adhere to the reporting timelines listed in section 18.9.

9.4 1st follow-up, 3- and 12-month follow-up

10 days to 4 weeks after insertion (= 1st follow-up), 3 and 12 months (±14 days) following the insertion, the patient returns to the investigational site for an in-office assessment of his/her BIOMONITOR III. The following procedures shall be conducted:

- Interrogate the BIOMONITOR III.
- Inspect the trend values for the R-wave amplitude (see section 9.5.1) and noise burden (see section 9.5.2) at each regular follow-up visit.
- Adjust patient specific program parameters, if applicable. Use the indication specific program settings (Go to `Parameters´ – `Program sets´ – `ProgramConsult´) if possible.
- **1st follow-up:** Program the periodic subcutaneous ECG recording in the `Patient profile´ tab of the HMSC and change cycle duration to 30 days.
- Store the electronic procedure data (including final device settings, measurements) of the BIOTRONIK programmer. Provide the programmer data by uploading the PDF-File via the ReportShare-function (see 4.7.1.11 and 9.5.4).
- P-wave measurements within the HMSC as described in section 9.5.3.
- **1st and 3-month follow-up:** ask the patient to answer the questions regarding the wearing comfort of the BIOMONITOR III
- **1st and 3-month follow-up:** check of insertion location and device migration (if applicable).

[10] Problem means any deficiency of the programmer or software or any adverse events related to the use of the programmer.

- Ask the patient to answer the questions regarding the usability of the Patient App, if applicable.
- Provide further details in case the patient was diagnosed (concerning the medical indication for the BIOMONITOR III).
- Answer questions regarding programmer and programmer software handling and document possible problems[11] regarding device programming.
- Answer questions regarding possible examinations by imaging techniques (MRI, mammography).
- Ensure that all source data from the 1st, 3-month and 12-month follow-up are documented, e.g. using a source data sheet which is recommended, and enter data in the respective eCRFs in the iMedNet EDC database.
- Document any adverse event or device deficiency observed during the follow-up by using the respective eCRF. Please adhere to the reporting timelines listed in section 18.

9.5 Description of measurements and other procedures performed at insertion and follow-up visits

9.5.1 R-wave measurement

The R-wave amplitude shall be measured after insertion and during all follow-up visits (see section 9.3.1and 9.4). The following steps need to be performed:

- Freeze, store and print the sECG window. In case of varying amplitude labeling, document both, the lowest and the highest amplitude value in the eCRF (Figure 11 and Figure 12).

Figure 11: Freeze screen during interrogation.

Figure 12: Document R-wave amplitude based on programmer screen or printout.

[11] Problem means any deficiency of the programmer or software or any adverse events related to the use of the programmer.

Note: It is possible that sensing is compromised by noise/artefacts immediately after the insertion procedure due to electrolytic properties of the anesthetics. In such a case it is advised to wait until the anesthetics have dissolved (~1-2 hours).

9.5.2 Measurement of noise percentage

The noise percentage shall be determined during all follow-up visits (see section 9.4). The following steps have to be performed:

- Go to 'Diagnostics' → 'Sensing' → 'Noise duration trend'. Put the caliper on the date of follow-up visit. Print. Document the noise percentage of the day of the follow-up visit.
- Freeze, store and print the sECG window as described in 9.5.1.

9.5.3 Assessment of P-wave visibility

The P-wave visibility shall be measured during all follow-up visits (see section 9.4). Assessment of P-wave visibility within the HMSC need to be performed as follows:

1st follow-up

At the day of 1st follow-up, check the first periodic sECG episode that was successfully transmitted to the HMSC. In patients with sinus rhythm, evaluate the number of expected P-waves (i.e. number of complete heart cycles) and P-waves that can undoubtedly be identified.

Check also the latest periodic sECG episode which was successfully transmitted to the HMSC.

In patients with sinus rhythm, evaluate the number of expected P-waves (i.e. number of complete heart cycles) and P-waves that can undoubtedly be identified.

3-month and 12-month follow-up

Check the periodic sECG episode which was successfully transmitted to the HMSC and, which is closest to the 3-month and 12-month follow-up date.

In patients with sinus rhythm, evaluate the number of expected P-waves (i.e. number of complete heart cycles) and P-waves that can undoubtedly be identified.

Enter the dates and values in the follow up SDS. Provide a PDF file export (StatusReport) from the HMSC with the respective episodes and upload the PDF-Files via ReportShare. Alternatively, the PDF files can be sent to the study e-mail address [redacted]

In addition an independent core laboratory will compare the P-wave visibility between the 48-hour Holter-ECG device and the sECG from the BIOMONITOR III. For this, the investigational site needs to conduct a 48-hour Holter-ECG and BIOMONOITOR III read out according to section 9.6.

9.5.4 Data Transfer via Report Share

During the study, programmer data containing all measurements have to be provided to the sponsor for insertion and each follow-up. Furthermore programmer data should be provided also for interim visits of the patient at the study site.

Note: We strongly recommend using Report Share function to facilitate the data transfer to BIOTRONIK.

Automatic export

Pre-setting of Renamic Programmer: open the 'Options' dialog in the Data Manager.

Activate the automatic upload by enabling the 'Automatic export' (3) checkbox (see Figure 13).

After implantation or FU was performed: click 'end' to close the application.

The upload will start automatically.

Or Manual export

Pre-setting of Renamic Programmer: open the 'Options' dialog in the Data Manager.

Activate the manual upload by enabling the 'HMSC export' (2) checkbox (see Figure 13).

Select one follow-up from Data Manager.

Click on 'Preview' and select all checkboxes.

Click on 'Export'.

Figure 13: Interface for the export of programmer data to HMSC via ReportShare.

In case that ReportShare is not available, e.g. for organizational or technical reasons, the following alternatives may be used for delivery of programmer data:

- Delivery via email to [redacted]
- Delivery via USB flash drive

For every export it has to be ensured that data are pseudonymized.

9.6 48-hour Holter ECG recording

48-hour Holter ECGs are to be recorded from all patients. It is recommended to start recording immediately after the completion of the 1st follow-up.

9.6.1 Initiation (start day)

1. Preparing the BIOMONITOR III
   - Set the clock on the programmer device to the precise local time.
   - Delete statistics and episodes (`Recordings´ → `Restart"). This sets the clock of the BIOMONITOR III.
2. Preparing the Holter ECG
   - Label flash card with patient ID and date.
   - Insert batteries (take a new one for every patient!).
   - Insert Flash card.

- Set the clock of the Holter ECG device to the precise local time (via `Set up´ → Time; navigate with yellow button and enter with green button).
- Select `Start Week´ via menu.
- Speech recording (in menu select `record´ and enter with green button).

3. Applying the Holter ECG device

- Attach three ECG electrodes according to Figure 14.

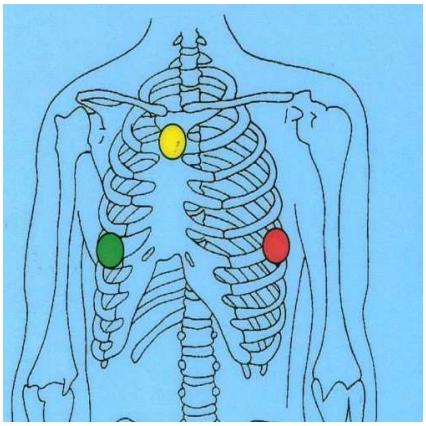


Figure 14: Electrode position for Holter ECG.

- Ensure ECG does not alter with change in position/posture.
- Reposition electrodes in case of ECG instability/poor quality.
- Start recording (with green button).
- ECG signal can be displayed by simultaneous pressing of the green and yellow button.
- Use neck lanyard, shoulder pouch or belt clip to attach recorder.

9.6.2 Completion (after 48-hours, end day)

1. Removing the ECG-device

- Stop recording by pressing the green button.
- Detach electrodes and remove ECG recorder.
- Remove battery and CF card.

2. Interrogate BIOMONITOR III

3. Providing data to the sponsor

- Download programmer data on USB stick (xml und pdf) and upload the PDF-Files via ReportShare. Alternatively, the PDF files can be sent to the study e-mail address [redacted]. Make sure the PDF file contains the "episode list".
- Send CF Card to:

  [redacted]
  BIOTRONIK SE & Co. KG
  Center for Clinical Research
  Woermannkehre 1
  12359 Berlin, Germany

9.7 Explantation/Deactivation

Explantation(s)/Deactivation and possible additional insertion (s) of the BIOMONITOR III have to be documented in the 'Explantation/Deactivation eCRF'. 'Deactivation' refers to the permanent decision not to use the information from the BIOMONITOR anymore. This is analog to an explantation, in case it is decided that the device will not be explanted for any reason (e.g. patient preference).

Fill in an Adverse Event eCRF and/or Device deficiency eCRF, if applicable. Fill in the 'Termination eCRF'. Explanted BIOMONITOR III devices need to be returned to BIOTRONIK for analysis whenever possible.

9.8 Interim follow-up

An unscheduled interim follow-up may occur anytime during the course of the study. It is not required to document the data on an eCRF. Only in cases where adverse events and/or device deficiency occurs this must be documented on the AE-eCRF.

9.9 Termination and post treatment

The `Termination eCRF' must be completed to document time and reason for study termination for each individual patient. In case of study termination due to BIOMONITOR III explantation or deactivation the `Explantation/Deactivation eCRF' must be completed. Regular study termination is after completion of the 12-month follow-up. The patients shall be informed at this last follow-up about their Master study termination.

The approach to patient follow-up as described in standard guidelines for ICM therapy, with respect to visit frequency and the nature of follow-up visits, are adequate for all patients after either regular or premature study termination.

9.10 Description of those activities performed by sponsor representative

Sponsor representatives will support the investigator during insertion or follow-up procedures if this is part of the clinical routine. They might also support the investigator by programming the ICM. Nevertheless, the investigator and the trained study team are responsible for the adherence to the study protocol.

Monitoring will be performed by a sponsor representative according to the monitoring plan. Qualified sponsor representatives from BIOTRONIK may support the investigator and study nurse in downloading and sending programmer data to CCR as part of their general technical assistance service.

9.11 Responsibilities

9.11.1 Responsibilities of the sponsor

The sponsor of the BIO|MASTER.BIOMONITOR III is:

BIOTRONIK SE & Co. KG

Woermannkehre 1

12359 Berlin

Germany

The sponsor ensures that all documents, information and necessary human resources are made available for initiation, conduct and termination of the study.

In addition, the sponsor is obliged to fulfill the following tasks (selection of items):

- Maintaining insurance cover or indemnification of subjects in case of injury in accordance with applicable laws.
- Contracting of investigational sites and investigators, specifically determining the agreement between sponsor and the research site with respect to such as but not

limited to the following: conducting the contract research, obligations of the sponsor/the investigational site/the investigator, fee payments of the sponsor, intellectual property and publication of research results, confidentiality, insurance coverage and compliance with applicable laws/regulations and ethical standards. Selection of suitable investigational sites, investigators and clinical monitors.

- Obtaining of a favorable ethics vote(s) for conduct of the clinical study.
- Obtaining approval of the involved competent authorities (if applicable).
- Responsibility for all payments and financial coverage of the study.
- Supervision of study conduct according to the legal regulatory requirements and the requirements of the CIP.
- Fulfill reporting duties of the sponsor to the ethics committees and regulatory authorities.
- Data analysis and data management.
- Performance of on-site audits as planned routine audits, on demand in case of detected non-compliances, or as preparation for an announced inspection by a Competent Authority.
- Provision of the final clinical investigation report (CIR) in accordance with applicable legal requirements and ethical principles.

9.11.1.1 Project management

The clinical project manager is responsible for the following (selected items):

- Development of the clinical investigation plan and possible amendments.
- Coordination of all study-related activities dedicated to the sponsor.
- Support of investigational sites during the study (obtaining ethics committee votes, etc.).
- Continuous information of investigational sites and clinical monitors on study progress.
- The clinical project manager is supported by other staff members of the sponsor (e.g. in-house clinical research associates, data assistants, database managers).

9.11.1.2 Data Management

The data manager is responsible for the following items (selection of items):

- Development and maintenance of the clinical data management system (CDMS; iMedNet of the company MedNet Solutions Inc, Minnetonka, MN 55305 USA).
- Development of the data management plan.
- Development of the eCRF user guide.
- User and roles management.
- Data management (final data quality check and release of clinical data).

9.11.1.3 Biostatistician

The statistician is responsible for the following items (selection of items):

- All statistical aspects within the clinical investigation plan.
- Statistical analysis for clinical investigation report.

The statistician will be supported by other staff members of the sponsor.

9.11.1.4 Monitor

The sponsor names clinical monitors for each participating investigational site prior to initiation of the respective site. Names and contact data will be provided to the investigational sites in

due time. In case of changes, the investigational site will be informed by the sponsor. An adequate monitoring will be ensured by the sponsor. Monitoring will be conducted according to the SOPs of the sponsor. Responsibilities of the clinical monitors are described in section 10 of this document.

9.11.2 Responsibilities of the investigators

9.11.2.1 Coordinating Investigator (CI)

The clinical study BIO|MASTER.BIOMONITOR III is coordinated by:

The responsibilities of the CI are listed in the following:

- Development and review of the clinical investigation plan.
- Procurement of the central vote of an ethics committee.
- Performance and progress control of the study.
- Continuous assessment of the risk/benefit ratio.
- If necessary, decision on premature study termination in consultation with the sponsor.
- Contribution to coordination of publication and presentations of study results.
- Advising all investigators in medical questions related to the study or study conduction.
- Evaluation of potential unexpected adverse events.
- Discussion of possible interim results.
- Cooperation in writing of the final clinical report.

The Coordinating Investigator is supported by the clinical Project Manager and other members of the sponsor. In addition, the CI has the same rights and duties as other principal investigators.

9.11.2.2 Investigator

The study shall be conducted by qualified investigators.

Rights and duties of the investigators are specified in the clinical investigation plan and are further regulated in the contract for study conduct. The principal investigator named in the study contract may share the rights and duties with investigators and other staff at the investigational sites. Nevertheless, the principal investigator retains the main responsibility for proper study conduct with respect to the following duties:

- Registration of the study to the bodies responsible for the investigational site (e.g. hospital administrative department).
- Notification to competent authority (if applicable) responsible for the investigational site.
- If required, obtaining of a positive vote of the ethics committee responsible for the investigational site.
- Adverse Event reporting according to the clinical investigation plan.
- Recruitment of suitable patients in an adequate time frame.

- Patient information and obtaining of written informed consent of the patient according to the requirements of the CIP.
- Safe and efficient use of devices.
- Inform the sponsor about new study team members before authorizing them for study related activities.
- Provide the sponsor with required documentation for assessing the qualification of study team members.
- Authorize co-investigators only after documented adequate study specific training.
- Discourage patients to consent for other interventional clinical investigations, in case the investigator is aware of such intentions beforehand. Inform the sponsor and follow the sponsor´s guidance, in case a patient has already been enrolled into another interventional clinical investigation. Obtain the sponsors permission before enrolling the patient into another interventional clinical investigation.
- Conduct of the study according to the CIP.
- Data collection and data entry in accordance with the requirements of the CIP.
- Providing supporting material, if necessary.
- Submission of safety reports and protocol deviations to ethics committee and competent authorities (if applicable).
- Support of monitoring and auditing activities.
- Confidential treatment of all study-related documents and information.
- Safeguarding the rights of the physical and mental integrity as well as the privacy and the protection of the data of the study patients.

In case the principal investigator (or authorized staff) does not fulfill the requirements defined, the sponsor is entitled to exclude the respective investigational site or principal investigator from further study participation.

9.11.3 Responsibilities of the Core laboratory

For the clinical study a core laboratory is contracted for assessment of Holter ECGs. The responsible core laboratory is:

[redacted]

The core laboratory is responsible to identify true arrhythmia episodes in the external Holter ECG.

The corelab will determine the following:

- Arrhythmia detection performance of the sECG

9.12 Possible influencing factors on outcome or interpretation of results

No factors that could influence the outcome or interpretation of the results are known at this time.

10 MONITORING PLAN

The responsibility of BIOTRONIK as sponsor is to ensure protocol and regulatory compliance through proper monitoring of the study. BIOTRONIK is required to ensure that the BIOMONITOR III 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 clinical investigation plan, applicable laws, local regulations and any conditions of approval imposed by the reviewing IRB/EC.

The entries in the eCRF will be reviewed and source data verified at the investigational site by monitors (authorized BIOTRONIK personnel, Clinical Research Associates – CRAs, or by authorized BIOTRONIK designees) to ensure that the investigator and the clinical investigation team conduct the clinical investigation in accordance with the CIP, the Declaration of Helsinki, ISO 14155, and applicable laws and regulations to ensure adequate protection of the rights, safety and wellbeing of subjects and the quality and integrity of the resulting data.

A monitor will visit the study site periodically during the study. All actively enrolling sites will have at least an initiation visit, one early monitoring visit after the first patients have been enrolled in order to detect and prevent systematic errors in study conduct or documentation, and a close-out visit. Additional monitoring visits will be conducted based on risk related criteria such as e.g. recruitment rate and documentation quality. Details on criteria for initiating monitoring visits as well as strategy and extent of source data verification are subject to a detailed monitoring plan developed by BIOTRONIK as an internal document.

Monitoring visits will assure, amongst others, that the facilities are still acceptable, that the CIP is being followed, that the EC/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.

Assessments of the study site will include but will not be limited to the following:

1. Completion and submission of the required electronic case report forms (eCRFs) and other applicable study documentation
2. Continued acceptability of the facilities, including storage and maintenance of investigational inventory
3. Adherence to the clinical investigation plan
4. Adherence to current version of ISO 14155 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 investigational site (see sections 14 and 20).

11 STATISTICAL CONSIDERATIONS

11.1 Statistical design, method and analytical procedures

The BIO|MASTER.BIOMONITOR III study is a prospective, single-arm, non-randomized, and open clinical study.

For the primary hypothesis - as described in section 7.2 – an one-tailed exact binomial test is carried out and the corresponding confidence interval for the SADE-free rate will be calculated. For continuous variables, descriptive statistics (sum, mean, median, minimum, first and third quartile and maximum) will be calculated. For nominal or ordinal variables frequencies and proportions will be calculated.

All calculations will be carried out using SAS 9.4© (or upgrades) or S+ 8.2© (or upgrades). All statistical analyses will be decribed in detail in the SAP (statistical analysis plan).

11.2 Sample size

The sample size is calculated with the power procedure of SAS and is based on the primary endpoint (SADE-free rate).

An SADE-free rate of 97% is expected. With alpha = 2.5%, power = 90% and a one-sided hypothesis a sample size of n = 133 results (normal approximation). Taking into account a drop-out rate of 10% a preliminary sample size of n = 148 patients results. By assessing the sawtooth-shaped power curve (which is not monotonically increasing) for binomially distributed parameters the minimal sample size with power > 90% is 141 patients. Taking the 10% drop-out rate into account, a total sample size of n = 157 patients results.

11.3 Level of significance and the power of the study

The significance level alpha is 0.025, the power is set to 90%.

11.4 Expected drop-out rate

A drop-out rate of 10% of the total sample size was taken into consideration based on estimates taken from the BioMonitor 2 Master Study experience.

11.5 Pass/fail criteria

The clinical investigation is deemed to be passed, if the primary hypothesis H_0 is rejected.

11.6 Provision for an interim analysis

The main differences between BioMonitor 2 and BIOMONITOR III are limited to a reduced device size and a novel simplified injection-like insertion procedure. The focus of this study is primarily on the safety of the BIOMONITOR III system including the insertion procedure.

Therefore the primary endpoint is to evaluate the SADE-free rate related to the BIOMONITOR III and the incision and insertion tool set from insertion until the 3-month follow-up. When all enrolled patients have either completed the 3-month follow-up or their study participation has been terminated, the data for the primary endpoint are completed. At this point in time, an interim Clinical Investigation Report will be written. The content of this report will be pre-defined in a Statistical Analysis Plan.

Individual data collected in this study, which do not concern the primary endpoint, may be analysed before the study is completed. If they shall be published, the stipulations of section 21 apply. Safety reasons, the support of regulatory submissions and publication opportunities may trigger unscheduled interim analyses.

Such unplanned interim analyses and reports, if any, will contain at least descriptive statistics of baseline and insertion data and descriptive statistics of the defined endpoints. Inferential

statistics of endpoints may be included to support publication activities. The precise scope of each interim analysis will be defined in the SAP before the individual interim analyses.

In case of a suspension of the clinical investigation, an interim analysis will be performed to generate a clinical investigation report according to the MDR requirements. No multiplicity adjustment is foreseen.

11.7 Termination criteria

As this study is part of the overall post-market clinical follow-up plan, no termination criteria are pre-defined for the study based on statistical considerations.

Criteria and procedures for suspension or premature study termination are defined in section 20.

11.8 Procedures for reporting of deviations to the statistical plan

A separate Statistical Analysis Plan will be finalized after database-go live and can be updated before database closure. Any deviation from the final version of the Statistical Analysis Plan will be indicated in the Statistical Analysis Report and Clinical Investigation Report.

11.9 Specification of subgroups

No subgroups are defined.

11.10 Procedure for accounting of all data for analysis

All data to be analyzed by descriptive and inferential statistical methods is entered in a clinical data manegemnt system (CDMS) by the investigators via the elctronic data capture system (EDC) iMedNet (MedNet Solutions, Inc. USA). Exports from the database will be analyzed with common validated statistical software packages (e.g. SAS or R) for accounting of the data. Due to adherence to the monitoring plan, data acquisition is ensured.

11.11 Handling of missing, unused and spurious data

Missing or spurious data will not be imputed and not be used for analysis. More details will be specified in the SAP.

11.12 Exclusion of data from confirmatory data analysis

In the following cases, data are to be excluded from analysis of the primary endpoint:

- No data are allowed to be collected and included in the absence of a documented consent.
- Data of patients will be excluded from analysis in case a patient terminates the study prior to any insertion attempt.
- Patients without primary endpoint but premature study termination earlier than 77 days after insertion (91 days = 3 month minus 14 days tolerance) are not included in the analysis set to avoid an over-estimation of the SADE-free rate.
- Any event that occurred later than the pre-specified time window for the 3-month follow-up in patients who did not have a 3-month follow-up (91 days plus 14 days tolerance = 105 days) does not contribute to the primary endpoint.
- SADEs will be adjudicated by an internal adjudication board, whereby the investigator assessment of seriousness and device relatedness will be re-examined.

Details are provided in the Statistical Analysis Plan.

11.13 Minimum and maximum number of patients per site

To minimize site-specific bias, the maximum number of patients per center will be n=30.

12 DATA MANAGEMENT

12.1 Data protection

According to corresponding national laws the patient must declare in the Informed Consent Form (ICF) that he or she agrees to the recording of his or her medical data and their pseudonymized transfer to the sponsor, any committee (if available), and, if necessary, to responsible Ethics Committees (EC) and Competent Authorities (CA). The patient agrees that authorized personnel or designees of the sponsor and the involved EC or CA (if applicable) may gain insight in the patient file to ensure that the patient was adequately informed about the clinical investigation and that the clinical investigation plan was followed properly.

All patient-related data and information received from the clinical study will be handled confidentially. The collected data will be transmitted to the sponsor and if necessary to the external assessment committees (e.g. CEC) for electronic data processing, safety reporting and analysis in compliance with the data protection law. The data will be pseudonymized at the sites before transmission, without using patient initials, to ensure traceability of data, but preventing unauthorized identification of individual patients. All clinical data will be stored in a validated system environment with adequate protection against unauthorized access. Insight will be given to responsible EC and CA upon request.

All involved parties, including subcontractors, are bound to data privacy according to the applicable data protection law. All patients will be informed on all relevant regulations concerning data secrecy and data protection which are applicable for the BIO|MASTER.BIOMONITOR III study in the patient informed consent form. Specifically, all 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 and date of informed consent is entered, will remain at the investigational sites. No copies of the patient identification log sheet 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.

12.2 Data collection

All study-relevant patient data will be documented pseudonymously in electronic case report forms (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 current 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 1, HIPAA and EU GDPR).

Use of the clinical data management system (CDMS) will allow 24 hours 7 days a week access to the module. The PI as well as those co-investigators to whom the PI delegates data entry and authorization of eCRFs need to be trained on iMedNet. After appropriate documentation of the training, user access is granted. 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 eCRF 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 source data verification. Exceptions for which the eCRF entry can be regarded as source data are indicated in section 10 as well as in the Monitoring Plan.

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

After data entry into the Clinical Data Management System (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 by automatically (CDMS) and manually (clinical monitor, clinical data manager) generated data queries and deviation forms.

The investigational site is obliged to answer all incoming data queries and deviation forms 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.

Prior to the final data analysis, all endpoint relevant data are checked for consistency and plausibility in a blinded way by the biostatistician.

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

The Clinical Data Management System (CDMS) is hosted on a dedicated database server at the vendor MedNet Solutions, Inc. Only authorized users with fixed roles have access to the Clinical Data Management System (CDMS). The access is controlled and maintained by the Clinical Data Management. 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 and the audit trail and other relevant CDMS contents 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 Site 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 files) adequate actions have to be taken to ensure data availability during the whole archiving period.

13 AMENDMENT PROCEDURES

If throughout the course of the study changes to the Clinical Investigation Plan (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 Investigator. All principle investigators have to acknowledge the receipt of an amendment by either signing the CIP acknowledgement page which is part of the CIP, or by signing the amendment agreement form if no new version was created.

Before implementation of any changes, substantial amendments have to be approved by the Ethics Committee (EC) and – if applicable – by the Competent Authority (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 **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 and applicable laws, 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. Otherwise they are **minor** 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.

Under **emergency** circumstances, deviations from the CIP to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor and the ethics committee.

No waivers from the CIP are allowed.

14.2 Recording, reporting and analyzing deviations

All deviations are recorded and reported electronically in the CDMS system iMedNet. If the eCRF logic has detected a CIP deviation based on the data entry, deviation forms are triggered automatically by iMedNet. Additionally, deviation forms can be created manually via iMedNet by the site or by the sponsor personnel.

14.2.1 Site specific deviations

Investigational sites are obliged to record any deviation immediately 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 assessed for the need of corrective or preventive actions.

14.2.2 Other deviations

Deviations by sponsor personnel or third parties shall be reported immediately to the sponsor by anyone who becomes aware of it. They are recorded in the CDMS system iMedNet, and assessed for the need of corrective or preventive actions.

14.2.3 Reporting

Deviations are reported in the interim and final clinical investigation reports.

14.3 Notification requirements and timelines

The sponsor records specific notification requirements of the involved ethics committees and competent authorities and assures that the required timelines are respected.

14.4 Actions

Actions are taken in order to repair or to avoid any negative consequences caused by a deviation. Furthermore, 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 report 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 in iMedNet and later 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 action would jeopardize the rights, safety or welfare of the patients.

15 DEVICE ACCOUNTABILITY

All devices used in this clinical study carry a CE mark and will be used within their intended use. Therefore special device accountability procedures are not applicable for countries located in the EU. However, the inserted BIOMONITOR III are identifiable by an unique serial number. This number will be recorded on the insertion eCRF form. By need or at least at the end of the study, a list with all used devices will be created.

Participating sites outside of the CE area will only use the devices after market approval or approval for the Master Study by the respective regulatory institution according to national regulations.

Note: The BIOMONITOR III as well as Remote Assistant III are not yet listed on the Australian Register of Therapeutic Goods. The study will be conducted under the CTN scheme in Australia. The devices provided to the investigators at Australian sites will be labelled as investigational devices and must not be used in routine care until TGA approval.

BIOMONITOR III which are not approved for an overall market release in non-EU countries and are labeled `exclusively for clinical investigation´ have to be stored under special conditions.

The sponsor keeps records to document the physical location of all investigational devices including the shipment of investigational devices to the investigational sites or to the local units, usage, storage and return. An electronic device accountability log is used for the documentation of the whole process.

Access to investigational devices is controlled and the devices are used in the clinical investigation only and according to the CIP.

The principal investigator or an authorized designee shall keep records documenting the receipt, storage, usage and return of the investigational devices. The electronic device accountability log is used for this site specific documentation.

The responsible field CRA checks the storage, usage and documentation and verifies the completeness of the device accountability log in the CDMS regularly during his/her visits.

After the closure of the study, the summary of this log will be used for the final report.

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). Each step in the clinical investigation, from the initial consideration of the need and justification for the study to the publication of the results, if any, will be carried out in accordance with recognized ethical principles.

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 14155:2011 "Clinical investigation of devices for human subjects – Good clinical practice".

In deviation to ISO 14155:2011, no dedicated Investigator's Brochure is provided to sites that accept CE mark, because the investigational device will only be made available after CE approval, and therefore the Instructions for Use (IFU) are considered as sufficient.

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

16.3 Ethics committee and competent authority

The study will not begin at an investigational site until favorable opinion of the responsible ethics committee has been obtained for that site and approval of the competent authority (if applicable) has been granted for the conduct of the study in the respective country.

16.4 Statement of adherence to additional requirements

If any additional requirements will be imposed by an ethics committee or a competent authority, 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.

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

A patient information form including the informed consent form has been prepared by the Project Manager. The content of this document needs to be reviewed and approved by the ethics committee, and suggested changes need to be implemented.

17.1 General considerations

The informed consent procedure is performed by the Principal Investigator or any investigator designated for this task as recorded in the delegation of duties 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. Special attention has to be paid to the individual information needs of the patient, and the appropriate methods used for the interview. The investigator has to verify that the patient has understood all information. The patient is given adequate time to consider his or her decision to participate in the clinical investigation.

When the patient agrees in the study participation, the patient personally writes the date and signs on the informed consent form. Afterwards, the investigator who performed the informed consent discussion writes the date and signs on the informed consent form. Both parties should sign on the same day. By signing the informed consent form, the patient is included in the study. Pre-screening of the patient chart in respect to the inclusion and exclusion criteria is not a study specific procedure.

Date and time of the informed consent discussion as well as date and time of patient's signature of the informed consent form should be documented in patient's medical record. A copy of the signed and dated written informed consent form is provided to the patient. Both signatures need to be obtained before any study related procedure. The investigator ensures that no subjects are included in this clinical study who are unable to give informed consent by selecting patients with age ≥ 18 years, who understand the nature of the procedure.

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.

Each informed consent form contains the emergency contact details for the respective principal investigator.

17.2 Special circumstances for informed consent

Not applicable.

18 ADVERSE EVENTS AND DEVICE DEFICIENCIES

In the course of the clinical investigation, undesired medical events can occur in participating patients, which are called adverse events (AEs) in the following. Furthermore, device deficiencies (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.

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

According to ISO 14155:2011 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 device. This includes:

- Events related to the investigational 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 devices.

Symptoms of the **known diseases** of the subject, like syncope with uncertain origin or atrial fibrillation, which were present already before participation in the study and do not change in frequency or severity during the course of the study are **no AE**. Also **planned** subsequent processing, like BIOMONITOR III explantation, implantation of a pacemaker, ICD or CRT device, or ablation, are **no AE**.

*see ISO 14155 3.2

18.2 Definition of adverse device effects

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

*see ISO 14155 3.1

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 and 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 serious adverse event to the investigational 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 device procedures without reasonable doubt.

The investigators will distinguish between 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 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 (serious) adverse events. In case of a replacement of the investigational device in response to an adverse event (e.g. lead replacement after dislocation), the replacement will be considered like an initial application of a new investigational device and shall be assessed accordingly.

An adverse event can be related both to the procedure and the investigational device. Complications of procedures are considered not related if the said procedures would have been applied to the patient also in the absence of investigational device use or its application.

18.3 Definition of device deficiency

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

*see ISO 14155 3.15

DDs of the investigational device shall be documented throughout the study. DDs which caused an adverse event 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 an 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 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 fetal distress, fetal death or a congenital abnormality or birth defect.

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

*see ISO 14155 3.37

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.

18.4.1 Patient death

If the death of a patient emerges during the study this SAE might be subject to special reporting requirements in some countries. Therefore as much information as possible should be provided to enable BIOTRONIK to explain the circumstances leading to the death. At least a pseudomized copy of the death records, an autopsy report (if performed) and a doctor´s letter detailing the medical history and the circumstances of the death should be sent to BIOTRONIK promptly.

On the AE-CRF the following information should be provided, if available:

- cause of death
- date and time of death
- place death occurred
- device status at the time of death
- statement whether the event was device or study procedure related

In addition to the adverse event eCRF a study termination form has to be completed.

Whenever possible, devices that are explanted must be returned to BIOTRONIK SE & Co. KG for analysis.

18.5 Definition of serious adverse device effect

An ADE* that resulted in any of the consequences characteristic of a serious adverse event (see section 18.4) is considered an SADE.

*see ISO 14155 3.36

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.

*see ISO 14155 3.42

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

The following peri- or post-operative risks are anticipated with the insertion and also during the post-insertion phase including explantation of the BIOMONITOR III and are therefore assessed as adverse device effects. They are listed in Table 4 as sorted by their incidence rates. For all references used for this chapter, refer to the list at the end of this section. In addition to the planned ICM insertion patients will undergo a non-invasive 48-hours Holter-Monitoring. Risks of Holter-Monitoring are rare but may include skin irriation at the application site of the adhesive electrode patches.

Table 4: Anticipated AEs based on literature research sorted by incidence rate.

Frequency	Event Type	Reference ID
Frequent 1 to 10 patients out of 100	Insertion site irritation/soreness	4, 9
	Insertion site erosion	3, 9
	Insertion site pain	1, 2, 3, 5, 8, 11
	Insertion site dehiscence/device protrusion/extrusion	2, 7, 13, 15
	Insertion site infection	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 15
	Insertion site hematoma	3, 7, 14
Occasionally 1 to 10 patients out of 1.000	Insertion site hemorrhage	1, 8, 13
	Insertion site discomfort	5, 12
	Insertion site bruising	2, 13
	Incision site complication	8, 13
	Device dislodgement/migration	3, 5, 13, 14
Not known Frequency not assessable on the basis of the available data	Oversensing, Undersensing, Premature battery depletion, Electromagnetic interference (EMI), Impaired healing, Insertion site rash, Non-insertion site rash, Non-insertion site pain, Numbness of upper arm, Procedural dizziness, Post procedural dizziness, Post procedural nausea, post procedural headache, Dyspnea, Vagal reaction, Presyncope, Supraventricular tachycardia, Shock/dyspnea (reaction to antibiotic administration prior to device insertion), Device interrogation issue, Home Monitoring transmission incomplete/missing, Housing surface conspicuous before implantation/insertion, Varying P/R values, Device in safety back-up mode, Silicone coating damaged, Foreign body rejection phenomena, Accumulation of fluid in the device pocket	1, 2, 3, 5, 6, 13, 16, 17

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18.8 Reporting responsibilities

18.8.1 Reporting responsibilities of the investigator to sponsor

The investigator shall document all events on the respective eCRF pages provided within the CDMS. The indicated timelines for reporting of initial cases and possible update reports shall be strictly followed (see section 18.9).

All AEs and ADEs) shall be reported together with an assessment by completing the AE-CRF in accordance with ISO 14155:2011.

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 Events either as long as the patient participates in the study, the clinical investigation is terminated prematurely or until the event has been resolved, whatever comes first. Ongoing SADEs related to the investigational device will be followed for a maximum time period of either 4 weeks after pre-mature or regular study termination of the individual patient. This also applies to Adverse Events involving the explantation or replacement of an investigational device, heart transplantation or implanation of a ventricular assist device. This follow-up period is reduced if 'Last Patient Out' is announced in the study. All follow-ups on open adverse events will stop at this point in time at the latest.

Multiple events may occur simultaneously in one subject. For each medically independent event 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 this might be subject to special reporting requirements in some countries. Therefore as much information as possible should be provided to enable BIOTRONIK to explain the circumstances leading to death. At least a pseudomized copy of the death records and an autopsy report (if performed) should be sent to BIOTRONIK promptly. 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 competent authorities (CAs) and ethics committees define specific safety reporting requirements. Investigators have to ensure, that they fulfil these local reporting obligations given by their competent authorities and ECs/IRBs, in case they are more restrictive than the general requirements stated in the section reporting timelines below.

18.8.3 Reporting responsibilities of the sponsor

BIOTRONIK SE & Co. KG will report all serious Adverse Events (SAEs)/Serious Adverse Device Effects (SADE) and all Device Deficiencies with SADE potential to the competent authorities depending on the local regulatory requirements.

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

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

18.9 Reporting timelines

The reporting timelines for the investigator are displayed in Table 5.

Table 5: Reporting timelines.

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

The obligation to assess and report SA(D)Es and Serious Device Deficiencies to the sponsor without unjustified delay is an important part of the Principal Investigator's responsibilities as defined by ISO 14155:2011. This obligation is not restricted to scheduled patient follow ups according to the CIP, but it is a continuous responsibility for the duration of the study, making sure that any unexpected risks originating from the study procedures or the investigational product are identified as soon as possible and patients are adequately protected. The Principal Investigator is responsible to set up appropriate workflows at his/her site, making sure that:

- the site study team is continuously informed on any relevant interactions or interventions concerning study patients at the site, regardless if members of the study team are directly involved or not;
- if the site is part of a larger organizational structure - e.g. a multi-faculty-hospital - a notification system is in place, making sure that other departments/clinics are aware of the patient's study participation and that relevant events, such as hospitalizations, are notified to the site study team without delay;
- if information on relevant events from external sources reaches the site (e.g. medical reports from other facilities), these are made available to the study team without delay.

Note: in this context the site is defined as the organizational unit (e.g. a hospital or a department/clinic within a multi-faculty-hospital), which serves as BIOTRONIK's contract partner for the study. Information that is part of the medical records hosted by the site is considered as known to the study team and subject to reporting.

18.10 Emergency contact

A contact address for patients in case of emergency will be provided in the individual patient informed consent forms.

In case technical support is needed the service hotline of BIOTRONIK is available 24 hours a day. Phone: [redacted]

18.11 Data (safety) monitoring committee

Not applicable.

19 VULNERABLE POPULATION

There are no health needs or clinical priorities for vulnerable populations which would justify the participation of these populations. Only legally competent patients shall be enrolled in this clinical investigation. Patients aged less than 18 years, pregnant or breast-feeding women and patients which are not able to understand the nature of the clinical investigation are excluded (see section 8.3.2 and 8.3.3). Therefore no provisions for vulnerable patients have to be arranged.

In case of

- incapacity acquired during study participation and either officially confirmed or assessed by the investigator or
- pregnancy, which is determined only after the start of study participation,

the patient should be excluded from study measures that go beyond routine care. Routine examinations / measurements or a further data collection can, however, be continued. Routine care can vary between sites and countries, but the following study measures have been identified as usually beyond routine care:

- 48-hour Holter ECG (see section 9.6).

20 SUSPENSION

20.1 Criteria and procedures

Suspension or premature study termination may occur due to several reasons:

- On behalf of the sponsor
- On behalf of the investigator
- On behalf of the EC

The sponsor is authorized to terminate the clinical study prematurely due to relevant medical/ organizational reasons.

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 arms, 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.
- Results from other clinical investigation 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. protocol violations).

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 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 and all enrolled patients of this decision.

If the EC 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.

20.2 Un-blinding procedures

Not applicable.

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 decision, additional requirements from the EC with respect to follow-up and data collection may apply.

If an event is ongoing at time of the last study related visit or study termination, whatever comes first, the outcome of the event has to be updated to 'Ongoing at study termination'. Ongoing SADEs related to the investigational device will be followed for a maximum time period of either 4 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 have to be informed on this procedure in written form in the patient informed consent form.

21 PUBLICATION POLICY

21.1 Decision for publication

The study will be registered in a publicly accessible database (e.g. clinicaltrials.gov).

All further decisions on publications will be made by the Publication Team, consisting of the Coordinating Investigator and member(s) of BIOTRONIK. In accordance with the good publication practice guidelines, it is generally planned to publish the study results also in case of negative findings. It is currently planned to submit at least an abstract to a congress OR a manuscript within 1 year after finalization of the clinical investigational report.

In case of realizing publications, the rights in regard to publication of the main results of the study, i.e. regarding the primary and secondary endpoints, belong to the Coordinating Investigator. The manuscripts and abstracts will be reviewed and approved by the Coordinating Investigator, all authors and BIOTRONIK.

21.2 Authorship guidelines

21.2.1 Purpose and validity

Purpose of this authorship guideline is to settle criteria which of the contributors to a publication should be identified as authors. It is valid for all contributors to a publication, including investigators, sponsor employees, and individuals contracted by the sponsor. All authors of a publication must fulfil authorship criteria listed below.

If the authorship criteria of the journal or the congress differ from these guidelines, the requirements of the journal or congress are to be respected.

21.2.2 Authorship criteria

Following the International Committee of Medical Journal Editors, authorship credit should be based on all of the following conditions:

- Substantial contributions to conception and design, acquisition of data (details are given below), 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 Publication Team will assure a fair assessment of the contribution of all potential authors. Especially, the Publication Team will weight contribution to the study data and the contribution to the publication idea and content of all potential authors.

Study specific criteria for *acquisition of data* have been defined. The following scoring system is valid:

- 1 point for each enrolled patients
- 1 point for each inserted investigational device
- 1 point for each patient, with complete and 100% compliant data set (i.e. absence of a major CIP deviation until regular study termination according to clinical investigational plan

21.2.3 Authors' tasks and responsibilities

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

First author:

- Guarantor for the integrity of the study and its publication

- Lead for writing and managing the publication
- Submit the publication to allocated reviewers (co-authors, BIOTRONIK etc.) according to the publication plan
- Preparation and submission of the publication according to timelines, defined in the publication plan
- Adaptation of the manuscript, based on Journal reviewer feedback
- Disclose potential conflicts of interest

Co-authors:

- Assist the first author in planning and writing the publication, if needed
- Review of the publication and give feedback within the determined time window
- Agree on the order in which they appear in the publication
- Agree on any changes in authorship
- Disclose potential conflicts of interest

21.2.4 Authorship of primary and ancillary publications

First authorship of the primary publication will be offered to the Coordinating Investigator. Investigators with the highest score will be considered for remaining positions. The authorship of ancillary publications will be based on contribution to conception and design of the publication, analysis and interpretation of data, the score, and authorship on previous publications.

21.2.5 Timelines and compliance

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 a reminder, a co-author may be invited to become first author. The Publication Team will ensure that authorship guidelines are met and authorship is attributed appropriately. The Publication Team will also track timeline adherence.

21.2.6 Reimbursement

No honoraria will be paid for authorship of publications.

21.3 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 a professional medical writer must also be disclosed in the acknowledgement section.

21.4 Ancillary publications

Ancillary publications are publications in addition to the primary publication. All study stakeholders (e.g. participating investigators, BIOTRONIK employees) may submit publication ideas through the Coordinating Investigator.

The Publication Team must approve ancillary requests and will need to ensure, that these publications do not present conflicts with other previously 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 Coordinating Investigator, all authors and BIOTRONIK.

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