Clinical Investigation Plan

for the

BIO|CONCEPT.BIOMONITOR III Study

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Date of CIP:	13-Nov-2018
Investigational devices:	BIOMONITOR III
	Remote Assistant III
	Programmer Software

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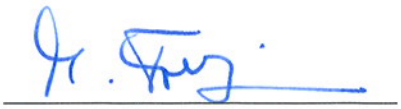
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List of principal investigators, investigation sites, and institutions

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
ASADE	Anticipated Serious Adverse Device Effect
bpm	Beats Per minute
CA	Competent Authority
CFR	Code of Federal Regulations der USA (www.gpoaccess.gov/cfr)
CI	Confidence Interval
CIP	Clinical Investigation Plan
CIR	Clinical Investigation Report
CCR	Center for Clinical Research; BIOTRONIK SE & CO. KG study department
CDMS	Clinical Data Management System
CE	CE mark, a stylized `CE´ (Conformité Européenne) placed on products to signify conformance with European Union regulations
CIP	Clinical Investigation Plan
CRA	Clinical Research Associate
CRF	Case Report Form
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	U.S. Food and Drug Administration
FIT	Fast Insertion Tool
FPI	First Patient In
FU	Follow-up visit
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HIPAA	Health Insurance Portability and Accountability Act
HM	Home Monitorig
HMSC	Home Monitorig Service Center
HP	High pass
HVR	High ventricular rate
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	Insertable cardiac monitor
ID	Identification Number
IEGM	Intracardiac Electrocardiogram
IFU	Instructions For Use (user manual)
iMedNet	Web-based electronic data entry (EDC) system for clinical trials provided by MedNet Solutions Inc.
IRB	Institutional Review Board
ISO	International Organization for Standardization (www.iso.org)
ISO14155	ISO standard no. 14155 `Clinical investigation of medical devices for human subjects — Good clinical practice”
LPI	Last Patient In
LPO	Last Patient Out
MByte	Megabyte

MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging
NSW	New South Wales
PAC	Premature Atrial Contraction
PDF	Portable Document Format
PI	Principal Investigator
PMCF	Post Market Clinical Follow-up
PSW	Programmer software
PVC	Premature ventricular contraction
QRS	Electrical complex on an ECG related to the depolarization of the ventricles
RAM	Random Access Memory
SaaS	Software as a Service
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAS	Statistics and Analysis Software produced by SAS Institute Inc. (www.sas.com)
SDS	Source data sheet
sECG	Subcutaneous Electrocardiogram
SOP	Standard Operating Procedure
SW	Software
TGA	Therapeutic Goods Administration
T-LOC	Transient Loss of Consciousness
TSI	Transmission Success Index
UBD	Used before date
UMTS	Universal Mobile Telecommunications System
USA	United States of America
USADE	Unanticipated Serious Adverse Device Effect
USB	Universal Serial Bus
VER	Validation Report
VES	Ventricular extrasystole
VIC	Victoria
Vs	Number of Ventricular Sensing Events

2 SYNOPSIS

Title	BIO|CONCEPT.BIOMONITOR III
Patient population	The patient population consists of patients in whom long-term cardiac rhythm monitoring may be required for diagnostic purposes.
Design	Open, prospective, single arm, non-randomized design
Investigational device(s)	• BIOMONITOR III implantable cardiac monitor, including incision and insertion tools • Remote Assistant III • Programmer Software (PSW 1901.A/S)
Objectives	The objective of this study is to assess the insertion procedure, use and handling of the incision / insertion tools and to assess the sensing quality of the BIOMONITOR III implantable cardiac monitor.
Primary / secondary endpoints	None
Data of interest	• Assessment of insertion procedure • Assessment of use and handling of insertion and incision tools • Assessment of R-wave amplitude • Collection of subcutaneous ECGs (sECGs) based on Home Monitoring over one month • Noise burden • Adverse events • Adverse device effects (procedure / device related) • Evaluation of P-wave visibility based on collected sECGs • Home Monitoring transmission success • Remote Assistant III trigger success
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 study and has provided written informed consent. • Patient is willing and able to perform all follow up visits at the study site. • Patient is willing and able to use the CardioMessenger and accepts the BIOTRONIK Home Monitoring concept.
Exclusion criteria	• Patients implanted with ICD or pacemaker. • Patient is pregnant or breast feeding. • Patient is participating in another interventional clinical investigation. • Patient is less than 18 years old. • Patient's life-expectancy is less than 6 months.
Study duration	~ March 2019 – June 2019 (approx. 4 months)
Sample size	up to 45 patients
Follow-up scheme	• Patient enrollment / baseline assessment with insertion procedure and pre-hospital discharge • 1-week follow up (in-office) • 1-month Home Monitoring Observation / study termination
Coordinating Investigator	A/Prof Justin Mariani The Alfred Hospital Department of Cardiology 55 Commercial Road Melbourne VIC 3004
Sponsor	BIOTRONIK Australia Pty. Ltd. Level 4, Building 2, 20 Bridge St Pymble NSW 2073 Australia

3 INTRODUCTION

Implantable Cardiac Monitors (ICMs) are devices which allow cardiac rhythm monitoring for a long time-period. Current devices have batteries that last up to three years. Therefore, 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 implantation 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.

Furthermore, ECG monitoring is crucial in assessing the efficacy of rhythm control therapies in patients with established AF. Since the distribution and duration of AF recurrences is often stochastic, ICMs play an important role in patients with infrequent symptoms and suspected arrhythmias. The capabilities of these devices open a wide field of diagnostic potential[4]. 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.

BIOMONITOR III - like its predecessor ICMs - 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 generational ICM, BIOMONITOR III, is the subject of this investigational study. 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 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.

4 INVESTIGATIONAL DEVICE

4.1 Summary description of the device and its intended purpose

4.1.1 BIOMONITOR III (ICM)

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. BIOTRONIK's major goal for this third generation ICM was to develop a significantly smaller device than the predecessor BioMonitor 2 , while retaining its industry-leading signal quality.

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 implantation.

The BIOMONITOR III system components are available in one variant only. This also applies to the incision and insertion tooling 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[5]. 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).

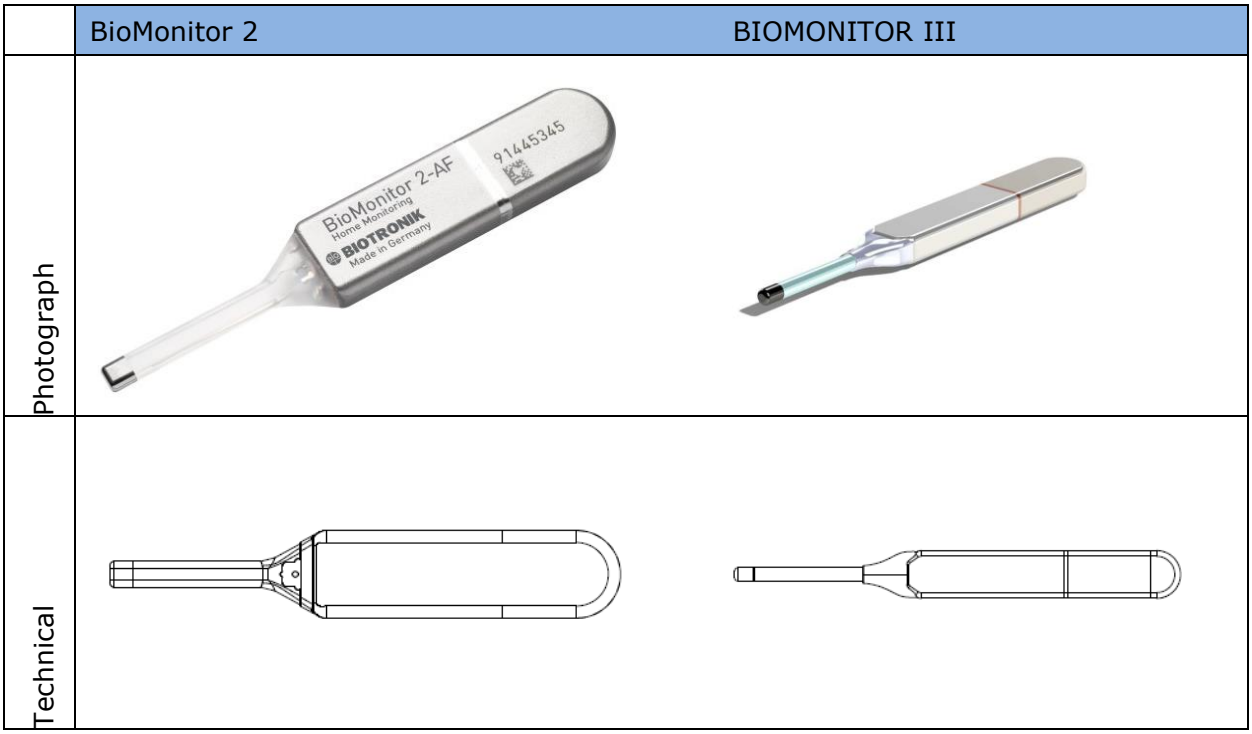


Figure 1: BioMonitor 2 (left) and BIOMONITOR III (right) consist of a similar rigid housing and a flexible electrode. BIOMONITOR III is miniaturized with respect to BioMonitor 2.

BIOMONITOR III the total length has been reduced to 7.7 cm, the rigid housing is 4.8 cm long, and the flexible part is 2.9 cm long. 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 detection algorithms of BIOMONITOR III are inherited from the predecessor devices BioMonitor 2, and before that, BioMonitor. Reliable detection algorithm performance has been confirmed through clip testing and through clinical study data of predecessor devices: (i) the BioMonitor Master Study[6,7]; (ii) the AF-Detect Study[8,9]; and, (iii) the BioMonitor 2 Master Study[10,11]. These studies are described in detail in Section 5.

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.

Data are stored in the implant, and recordings are transmitted via the CardioMessenger external device to the BIOTRONIK HMSC on a daily basis. The selection of appropriate data 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[12].

Patients with an implanted 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 [13].

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 4.7.2)

4.1.3 State of the art

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 2009) 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´[4]. Syncope accounts for 1-6% of emergency room visits and about 1% of hospital admissions[14]. 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[2]:

- 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 implantable cardiac monitors in comparison with `conventional´ investigations like tilt table tests, EP studies or adenosine triphosphate tests. For these reasons, ICM are becoming increasingly important in guiding a safe, specific and effective therapy for patients with unexplained and recurrent syncope and should be implanted early rather than late for the evaluation of unexplained syncope[15].

ICM can be safely implanted 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[16]. In addition, undiagnosed `silent AF´ is often suspected to be the cause of cryptogenic strokes[17–25]. In patients who have already had a stroke, identification of AF as the cause is critical to initiating proper therapy[26,27]. Early recognition of AF is critical for stroke prevention[28]. 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[29–31]. The routine use of cardiac monitoring to identify patients with paroxysmal AF who will benefit from anticoagulation has been reported to be cost-effective[32].

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[33]. The prevalence of AF increases with age, from <0.5% at 40–50 years, to 5–15% at 80 years[16].

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[16,33,34]. Various factors[35], 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[4,16,33,36,37].

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[6]. 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[38–49]. Therefore, especially to assess freedom from AF, continuous ECG recording is the gold standard[37,50–52]

Therapeutic strategies for AF may be preventing thromboembolism, minimizing symptoms, restoring sinus rhythm, and controlling the ventricular rate [16,33]. 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[53]. However, since many AF episodes are asymptomatic, and AF recurrences are often clustered and do not show a random pattern[4,37,54], 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[4,16,33,36,37,55–58].

4.2 Manufacturer

The manufacturer of the BIOMONITOR III system and all investigational devices is:

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

4.3 Model name including software version and accessories

The devices undergoing clinical investigation are the following BIOTRONIK devices:

Model Name	Model Number
BIOMONITOR III incl. Incision Tool and Insertion Tool (**FIT OneStep**)	436066
Programmer Software PSW 1901.A/S	445669
Remote Assistant III	435292

None of these devices has been approved for market release yet by a regulator or notified body. The devices provided to the investigators will be labelled as investigational devices and must not be used in routine care.

In addition, the following TGA approved BIOTRONIK devices will be used during the investigation:

Model Name	Model Number
Renamic programmer device	371960
CardioMessenger Smart 3G AU	401828

4.4 Description of traceability

All investigational devices are labeled for exclusive use within the clinical investigation and are identifiable by a unique 8-digit serial number. 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 an electronic document, the device accountability log (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 unused devices have to be returned to BIOTRONIK.

4.5 Intended purpose of the device in the study

The BIOMONITOR III system and all components will be used in the BIO|CONCEPT.BIOMONITOR III study within their intended use.

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

BIOMONITOR III is an implantable patient-activated and automatically–activated monitoring system that records subcutaneous ECG (sECG) and is indicated in the following cases:

- Patients at high risk of developing a clinically important cardiac arrhythmia
- The investigation of symptoms such as palpitations, pre-syncope or syncope, that are suggestive of an underlying cardiac arrhythmia
- For the detection of paroxysmal atrial fibrillation in patients presenting with cryptogenic stroke
- For the detection of paroxysmal atrial fibrillation in patients undergoing or who have had an AF ablative procedure

4.6.2 Contraindications of BIOMONITOR III

There are no known contraindications for the implantation of BIOMONITOR III. However, the particular patient´s state of health determines whether a subcutaneous device will be tolerated long-term.

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.

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 below (Figure 2). The total device length is 78 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. The rigid part consists of titanium housing and is coated with silicone.

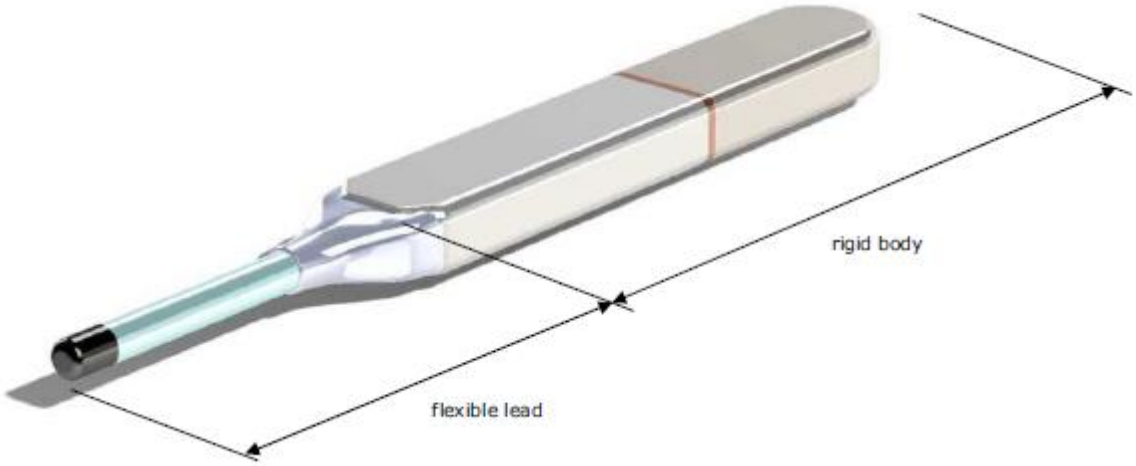


Figure 2: BIOMONITOR III shape and sensing vector

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 electrogram (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:
After high-pass filtering of the cardiac input signal (to extinguish respiratory signals and baseline fluctuations), a second high-pass filter is applied to suppress T-waves and P-waves of the morphology/unfiltered signal. The resulting signal (sensing/filtered signal) is compared against an adaptive sensitivity threshold and R-waves get markered as sensed ventricular event (Vs) accordingly. In order to exclude artefacts from arrhythmia evaluation, a noise-window is (re-)started with every R-wave sense to reveal high-frequency artefacts. Those are markered as Vn and have an inhibitory effect on arrhythmia detection. Additionally, also signals which are considered too low in amplitude and thus most probably not of cardiac origin, are marked as Vn.
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 of the previous sensed ventricular event (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, 60 seconds of ECG will be stored in the device memory.
The end of an asystole episode is detected when the Vs-Vs interval is shorter than the programmed asystole interval limit.

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.

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, 60 seconds of ECG will be stored in the device memory. Once Sudden Rate Drop is detected, the algorithm starts to detect termination.
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. 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 comparing the differences between consecutive pairs of R-R intervals with a stability threshold, which is adapted to the mean R-R interval and a stability limit.
Differences between R-R intervals exceeding the stability threshold are counted, and the analysis window is indicated as AF if the count reaches a detection threshold. AF status is detected when consecutive analysis windows (hysteresis) are indicated as AF. If the AF status is sustained over a confirmation time period, then the AF recording is triggered and the AF statistics are updated. The algorithm identifies the AF termination in a similar way, but with a separate set of programmable parameters.
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 limit, R-R variability limit, onset/resolution window, onset intervals, and resolution intervals.

4.7.1.7 Bigeminy rejection

The bigeminy rejection parameter of 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 `Standard´ settings, the algorithm rejects bigeminy rhythms that are very stable and repeatable. However, in some patients who are not in AF, the intervals demonstrate a slightly repeating bigeminy pattern or transition between different states of bigeminy (bigeminy, trigeminy or quadrigeminy). In these patients, the `Aggressive´ setting may be used to filter out these rhythms more completely 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 records 60 seconds subcutaneous ECG consisting of 50 seconds pre-trigger and 10 seconds post-trigger data. 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[9].

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 where minimal device movement due to positional changes or body and arm movement is expected (Figure 3). The left parasternal region (a) or a location between the suprasternal notch and the left nipple (b), generating an approximately 45 degree rotation from the midline, is preferred. In exceptional cases, a left sub-mammary position (c) can be selected.

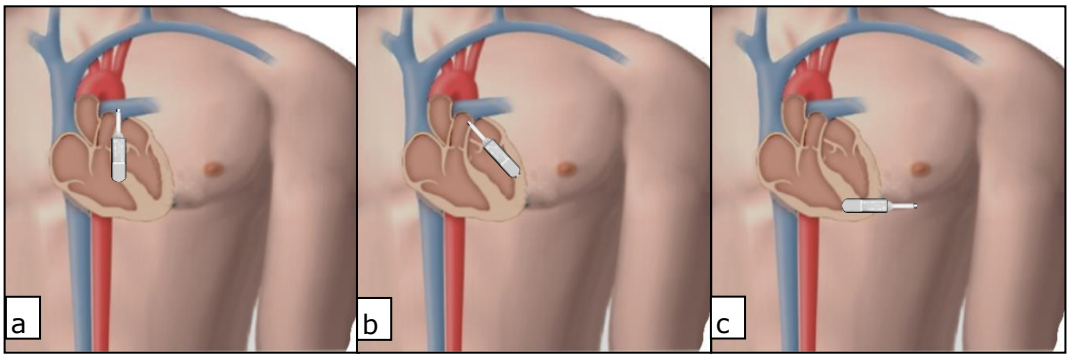


Figure 3: Example for possible positions of BIOMONITOR III

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.

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.

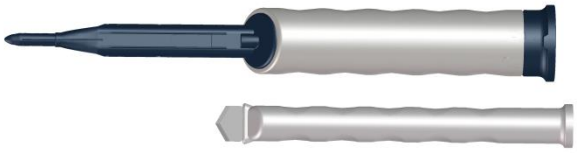
side view	top view
	

Figure 4: Incision tool and FIT OneStep insertion tool

Incision procedure:

The Incision tool has a blade of stainless steel which has two edges meeting at 110° (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, and the tool-blade pushed in at approximately 90° to the raised skin fold, so that the incision direction is parallel to the local body surface (Figure 5). The incision depth is limited to 10 mm by design and the physician is advised to consider the patient's anatomy.

Insertion procedure:

The FIT OneStep Insertion Tool allows injection like insertion of the implant using a single tool. 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. The FIT OneStep tool is inserted in the incision opening and then advanced within a sub-dermal plane until the tool handle approaches the skin incision, to create a tunnel for the BIOMONITOR III implant (Figure 6, upper row). 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. Whilst keeping the handle held in apposition with the skin of the insertion site, the tunneling end of the tool is retracted through the outer handle of the tool. As a result, the clam-shell tunneling tip of the tool is pulled back over the implant, leaving the implant within the subcutaneous connective-tissue tunnel (Figure 6, lower row).

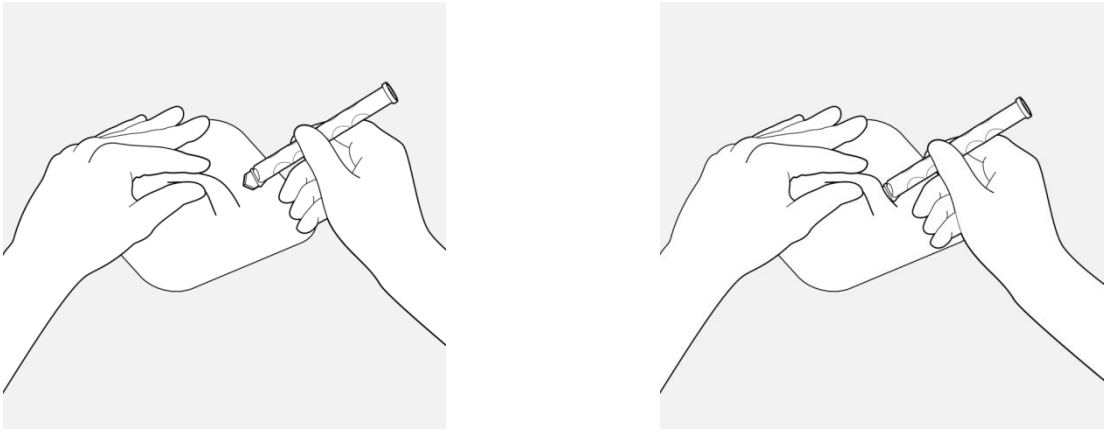


Figure 5: Insertion procedure: Handling of the incision tool

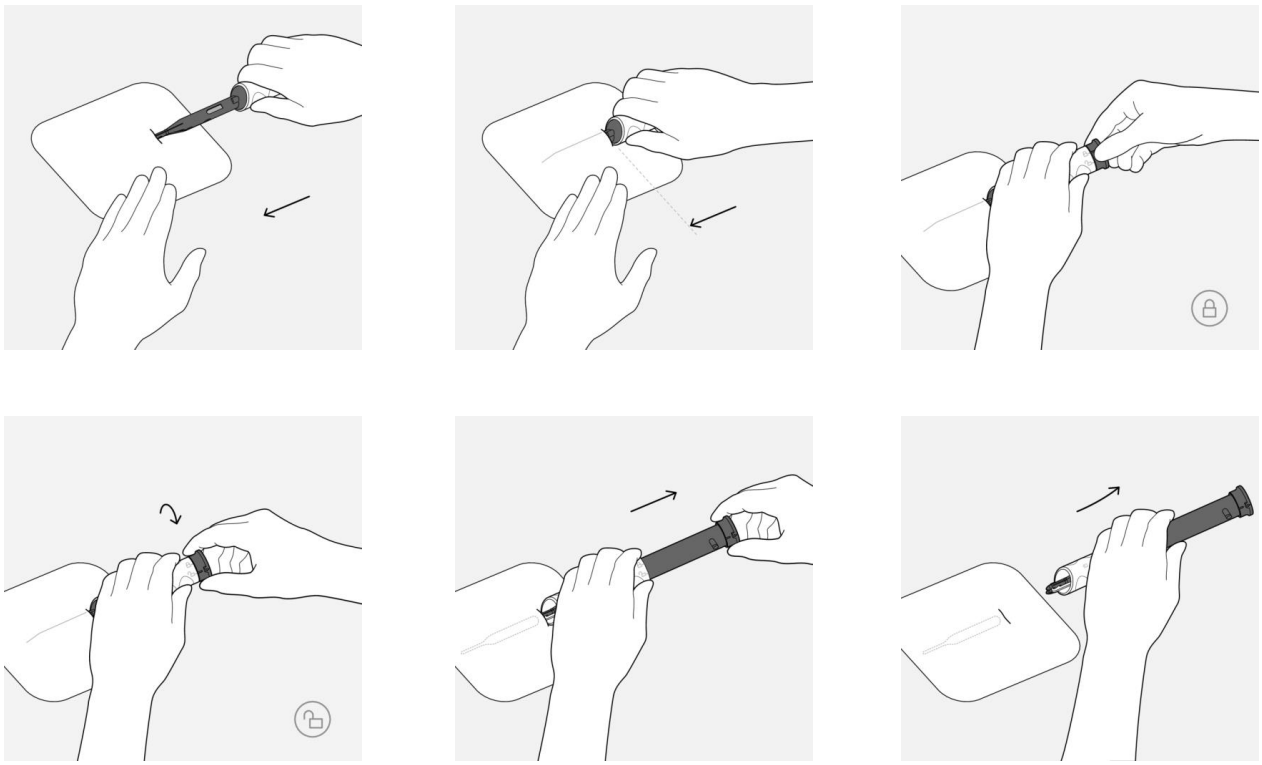


Figure 6: Insertion procedure: Handling of FIT OneStep and placement of BIOMONITOR III

For incision closure, standard clinical practice is advised. The protection of the wound from environmental influences, according to hospital guidelines, finalizes the insertion procedure of BIOMONITOR III.

4.7.1.11 Home Monitoring, ReportShare and BIOTRONIK 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.
ReportShare is software that allows the physician to upload follow-up 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 (Home Monitoring Service Center) and can be exported in a PDF-format (`CardioReport´).
Data transmission from the device is performed with a daily device message. Device messages that indicate special events in the heart or in the device are forwarded 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:

- Sustained atrial arrhythmias
- Sustained 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. However, the Patient APP software **is no emergency system.** In the event of an emergency or disturbances, the patient is asked to seek medical care and go to available medical facilities.

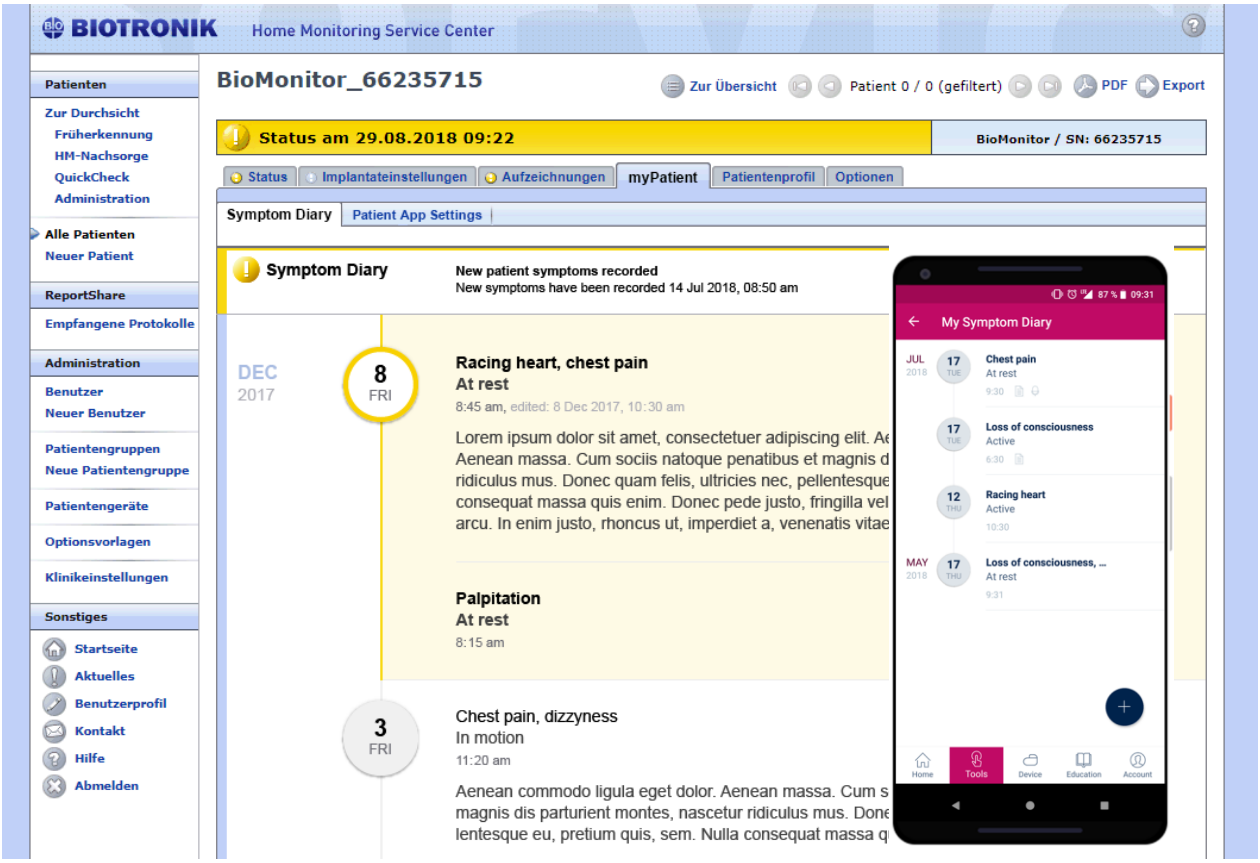


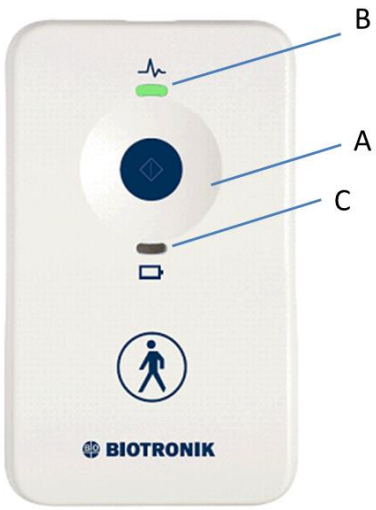
Figure 7: Symptoms diary as represented in HMSC and in the BIOTRONIK Patient APP

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 predecessors, by a small electronic user-device, the Remote Assistant III.



A) Record button

B) Telemetry status light

C) Low battery light

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 implanted 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 storage of cardiac data when a symptomatic event occurs or has occurred by applying the device over the location of BIOMONITOR III implantation, and pressing the record button (position A in Figure 8). When the record button is pressed, the Remote Assistant III indicates if telemetry with the implanted device was successful by means of a yellow light indicator, and the user gets feedback about successful recording by green light indicator (position B in Figure 8). A second indicator light on the Remote Assistant III (position C in Figure 8) indicates if its battery voltage is low.

4.8 Summary of training and experience needs

BIOMONITOR III is a medical implant intended for physicians who are familiar with the insertion of implantable cardiac monitors. In animal studies and tool-set testing in deceased bodies the insertion procedure was already investigated. However, the BIOMONITOR III has never been inserted in a living human being. Thus, during the initial insertions in this study, a representative of the sponsor will be present to give advice if needed and will train the investigator on the respective study procedures. The handling and insertion procedure are described in a respective guidance document.

The interrogation and programming of BIOMONITOR III shall only be done by appropriately trained personnel and using the BIOTRONIK programmer Renamic with the study-specific software release.

4.8.1 Description of medical and surgical procedures

BIOMONITOR III has to be inserted by a physician 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.

After completion of the insertion procedure the physician will perform wound closure according to the local clinical practice.

5 JUSTIFICATION FOR THE DESIGN OF THE CLINICAL INVESTIGATION

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 were adopted in BIOMONITOR III as previously discussed.

A more detailed documentation of all pre-clinical and clinical tests as well technical data of validation tests are documented in the investigator's brochure[59].

5.1 Pre-clinical data

5.1.1 Animal study

A 6-week GLP study was conducted in October to November 2018 to evaluate safety in a swine (Yucatan) model. A total of six (6) swine are enrolled in this study plus one spare. The spare shall be utilized if needed to replace animals lost to events that are unrelated to the BIOMONITOR III.

All subjects were assigned to an experimental treatment (BIOMONITOR III) and a control treatment (BioMonitor 2) thereby serving as their own controls. This design intends to reduce the total number of subjects required to perform the study and eliminate the effects of inter-subject variability when comparing test articles to control articles.

At the time of implant, the delivery tools were assessed for safety. Any events that may impair the functioning of the implant or injure the animal will be documented in the case report form(s) (CRF).

The final phase of the study, (6 weeks post-op ± 3 days) will consist of a non-survival, anesthetized data collection. All animals will be weighed prior to anesthesia and blood collection will occur while the subject is anesthetized but before any data is collected. Fluoroscopic examination in the AP/DV and lateral positions will be conducted. Attempts will be made to duplicate the angle and alignment of the fluoroscopic image to those used during the implant procedure. Toward this end, anatomical markers like the spinous processes, sternum, ribs, diaphragm, and heart will be utilized as references. Evidence of migration, erosion, or other unexpected effects will be reported at that time.

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+ implants per year for 3+ years), were recruited to participate in this validation study. Each participant completed four successful device insertions, resulting in a total of 60 successful 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 tasks evaluating the safety and usability of the Incision Tool, Fast Insertion Tool (i.e., FIT OneStep), IFU, and non-verbal reference guide.

The study included the tasks that were both a primary clinical functions and covered hazard-related scenarios with at least a low severity of harm (i.e., a severity rating equal or greater than two). The tasks included opening and removing the contents from the BIOMONITOR III package, preparing the tooling and device for insertion, defining and creating an incision for insertion, and implanting the BIOMONITOR III device.

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 understand any of the physicians' 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

5.2.1 BioMonitor 2 Pilot Study

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 implantation. Data of 30 patients from 5 Australian clinical sites from December 18, 2014 (first implant 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 implantations were performed successfully. The median insertion time was 2.5 min and the median of the total implantation 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 implantation tool set FIT1/2. The results have been published in an adequate scientific journal[60].

5.2.2 BioMonitor 2 Master Study

The 'BIO|MASTER.BioMonitor 2 Study' 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 is 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[10,11]. A publication is currently under review in a scientific journal.

5.2.3 BioInsight

The purpose of the BioInsight study 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[61] (95% CI: 0.3%, 9.5%).

5.3 Justification

The main objective of this study is to provide clinical data about the insertion procedure and the sensing quality of the BIOMONITOR III system. Clinical studies of the predecessor have shown that the concept of the implantable cardiac monitor is safe and efficient (see above). Prior to this first-in-man study the new insertion procedure of BIOMONITOR III was tested in an animal test study and in an insertion testing on deceased human bodies. The BIO|CONCEPT.BIOMONITOR III study will only be started, if both provided positive safety results.

The combination of a rigid and a flexible part, which yields a long sensing vector is a common design feature between BioMonitor 2 and BIOMONITOR III. Therefore the R-wave amplitude will be investigated as the main endpoint to confirm sensing quality. Since the main difference between BIOMONITOR III and BioMonitor 2 is in the insertion procedure, including the development of a new insertion tool set - the main focus of the study will be to assess insertion success and safety. Data from implantations 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.

As the BIOMONITOR III system will be used for the first time in clinical routine a significant number of patients (up to 45 patients) and about 15 experienced investigators shall be included in this feasibility study. The open, uncontrolled design without study-specific procedures or device settings was chosen to minimize bias compared to a routine care population. To cover a broad patient population enrollment will not be restricted to any subgroup or indication. 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. . Since the study device is used in the intended way, the study does not impact on the device longevity.

Adverse Events which are related to the insertion procedure typically emerge within the first days after insertion. Therefore a total study duration of 4 weeks is deemed sufficient for safety follow-up. A 1-week in-office follow up will be complemented with a 1-month Home Monitoring observation and a patient interview via telephone to reveal all possible device or procedure – related events. Possible related SAEs of the patients will be followed up for an additional 4 weeks.

6 RISKS AND BENEFITS OF THE DEVICE AND CLINICAL INVESTIGATION

6.1 Anticipated clinical benefits

By participating in this study, the patient receives a modern device with many clinical benefits. In addition, they will benefit from being intensively supervised throughout the course of the study.

The benefit of the utilising of ICM's in the management of syncope is proven in many studies (e.g. EaSyAS[62], ISSUE-2[63]). With ICM's, diagnostic yield is improved compared to conventional testing[64–68]. This improved diagnostic accuracy translates into the delivery of more specific therapy[14,15,69,70]. There is data to suggest that syncope burden can be reduced based on an early ICM based therapeutic decision[14,64,70,71]. In addition, ICMs aid in establishing the diagnosis of AF[40,48,72]. 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[73]. ICMs have also been successfully utilized in the assessment of various AF ablation therapies[35,48,74] . The ultimate goal of AF monitoring will be to guide the clinical management of AF patients[16,33,53]. 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.

Subjects who participate in this study might benefit from reduced noise level. Noise remains a significant problem amongst the current generation of ICMs. In a recent study[75] of a currently available ICM, only 55 percent of AF detections were confirmed as being AF. The large sensing vector of BIOMONITOR III is expected to yield a large QRS 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.

6.2 Anticipated risks

6.2.1 Anticipated adverse device effects

Adverse device effects anticipated for patients with ICM implantation are described in section 18.7 of this clinical investigation plan. Since no additional procedures outside the clinical routine care are required during participation in BIO|CONCEPT.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.

6.2.2 Residual risks associated with the device

In principle, technical failures in the implant due to component failures, or other events that could compromise functioning, cannot be ruled out; they are expected to 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

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 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 device, 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 device.

6.3 Steps to control or mitigate the risks

Risks associated with BIOMONITOR III which are mentioned above, as well as in section 18 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.

Nevertheless, a residual risk remains.

6.4 Risk-to-benefit rationale

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.

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

We therefore conclude that benefits of this study outweigh the risks.

7 OBJECTIVES AND HYPOTHESES

7.1 Objectives

The objective of this study is to investigate the safety and efficacy of the new insertion procedure and the use and handling of the incision and insertion tools. Additionally, the sensing quality of the BIOMONITOR III will be investigated.

7.2 Endpoints and hypotheses

There are no pre-specified hypotheses and all analyses are explorative only.

7.2.1 Primary / secondary endpoint and hypotheses

Not applicable.

7.2.2 Data of interest

Information will be collected to characterize the insertion of the BIOMONITOR III and the safety and efficacy of the BIOMONITOR III system. The data will be statistically analyzed, where appropriate (see section 11). Specifically, the following data of interest will be analyzed:

- Insertion success rate
- R-wave amplitude measured at insertion and at 1 week / 1 month after insertion.
- Noise burden at 1-week follow-up and 1-month Home Monitoring observation
- Adverse events and device deficiencies associated with insertion procedure and insertion tools
- Remote Assistant trigger success rate
- Home Monitoring transmission success rate

7.3 Claims and intended performance

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

Table 1: List of promotional claims related device features and study endpoint

Promotional Claim	Feature	Related endpoints / data of interest
- suited for any anatomy (even muscular, thin etc.)	BIOMONITOR III: Miniaturization, maintaining original rigid-flex design	Assessment of insertion procedure
- industry-leading high R-wave sensing (as prerequisite for reliable arrhythmia detection)	BIOMONITOR III: ~70 mm sensing vector	R-wave amplitude
- improved visual arrhythmia assessment due to P-wave visibility - x% P-wave visibility	BIOMONITOR III: - Lossless sECG-compression - long sensing vector - fractal coating - low HP-filter	Assessment of P-wave visibility

Promotional Claim	Feature	Related endpoints / data of interest
- fast subcutaneous injection-like procedure	Incision/Insertion Tool: complete tool-set with implant premounted	Assessment of insertion procedure
- highly reliable remote monitoring guarantees daily availability of important information through Home Monitoring - TSI of > 90%	BIOMONITOR III / HM: Daily Transmission	Home Monitoring transmission success
- Patient-individualized, indication-based, quick and accurate programming - rare need for re-programming/adaptation	BIOMONITOR III: Indication-based Program-Sets	Assessment of device programming
- Clinical rather than technical programming	BIOMONITOR III: Software User Interface	Assessment of device programming
- Highly sensitive syncope-diagnosis as the device is robust against oversensing - Highly specific syncope-diagnosis as the device is robust against undersensing, thus low review burden - State-of-the-art asystole detection (sensitivity, specificity, positive-predictive-value and negative-predictive-value) in combination with superior R-wave sensing	BIOMONITOR III: Asystole detection	Supportive episode data collection (Home Monitoring)
- Highly sensitive and the same time highly specific AF-diagnosis as the device is robust against over- and undersensing - High AF-specificity, thus low review burden - State-of-the-art AF-detection (sensitivity, specificity, positive-predictive-value and negative-predictive-value) in combination with superior R-wave sensing	BIOMONITOR III: AF detection	Supportive episode data collection (Home Monitoring)
- Highly sensitive and specific arrhythmia diagnosis as the device is robust against over- and undersensing - low review burden - State-of-the-art arrhythmia-detection (sensitivity, specificity, positive-predictive-value and negative-predictive-value) in combination with superior R-wave sensing	BIOMONITOR III: Brady-, HVR-, SRD-detection algorithms	Supportive episode data collection (Home Monitoring)

Promotional Claim	Feature	Related endpoints / data of interest
- reliable trigger functionality/ high successful trigger rate	Remote Assistant III: Patient-triggered episode-recording	Remote Assistant trigger success rate

7.4 Safety assessments

There will be assessments of risks and anticipated adverse device effects which are described in section 18.

7.5 Further data of interest

Additional information will be collected to characterize the study population and safety and efficacy of the investigational devices. The data will be statistically analyzed, where appropriate (see section 11). Specifically, further data of interest will include:

- Demographics including age, gender, weight and height
- Medical history
- Indication for device therapy
- Assessment of insertion procedure and insertion tool performance
- Assessment of device programming
- Assessment of P-wave visibility

8 DESIGN OF THE CLINICAL INVESTIGATION

8.1 General considerations

8.1.1 Type of clinical investigation

This is an open, prospective, single-arm, multi-site, non-randomized, explorative study, which will be conducted at Australian sites.

8.1.2 Measures taken to minimize or avoid bias

The study is conducted according to BIOTRONIK CCR Standard Operating Procedures which describe in detail measures and actions to minimize bias.

To avoid undue influence of single investigators of the evaluation of the insertion procedure, a high number of investigators (up to 15) shall take part in the insertions and contribute to a comprehensive assessment of the new insertion procedure. The maximum insertions per investigator are limited to 5. Exemptions will be communicated in written form in case enrollment is too slow.

8.1.3 Selection of measurements for endpoints

No statistical endpoints are defined.

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 will be documented on eCRFs. The corresponding time schedule is given in section 9:

- Enrollment / Baseline visit
- Insertion visit, incl. assessment of insertion procedure
- 1-week follow-up visit
- 1-month Home Monitoring observation and telephone interview
- Adverse Event form
- Device Deficiency form
- Study termination form

All data have to be available for source data verification during monitoring visits of the sponsor. Patients have to consent to the use of their medical data in the patient file prior to enrollment by signing the informed consent form. Information given on source data sheets, e.g. for documenting insertion procedure assessment (insertion visit) and the patient telephone interview (1-month Home Monitoring observation) is accepted as source data.

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 study and has provided written informed consent.
- Patient is willing and able to perform all follow up visits at the study site.
- Patient is not pregnant or breast feeding.

- Patient is not participating in another interventional clinical investigation
- Patient´s life-expectancy is not less than 6 months.

8.1.4.3 Patient demographics and medical history

After obtaining informed consent, the following information has to be entered in the baseline eCRF:

- Date of Enrollment / Baseline visit
- Demographic characteristics (age, gender, height, weight)
- Details on the ICM-indication of the patient
- Medical history of patient, medication

8.1.4.4 Insertion

After the insertion procedure the following information has to be entered in the respective eCRF:

- Date of insertion
- Serial number of BIOMONITOR III, CardioMessenger and Remote Assistant III
- Position and orientation of the BIOMONITOR III device
- Information on the insertion, handling of tools, including start time and end time of insertion procedure
- R-wave measurements (based on programmer screen)
- Device interrogation and provision of programmer download
- Adverse Event information
- Device Deficiency information

8.1.4.5 1-week follow-up

At the 1-week follow–up visit the following information has to be entered in the respective eCRF or provided via HMSC:

- Date of visit
- R-wave measurements (via HMSC)
- Noise rate measurements (via HMSC)
- P-wave visibility assessments
- Changes in device programming, if appropriate
- Device interrogation and provision of programmer download
- Adverse Event information
- Device Deficiency information

8.1.4.6 1-month Home Monitoring observation and telephone interview

The investigator is asked to consult the Home Monitoring Service Center (HMSC) one month after insertion and evaluate technical and diagnostic data. Additionally a telephone interview with the patient shall be conducted. The following information has to be entered in the respective eCRF or provided via HMSC:

- Dates of evaluated daily transmissions with periodic sECGs
- R-wave measurements (via HMSC)

- Noise rate measurements (via HMSC)
- P-wave visibility assessment
- Changes in device programming, if appropriate
- Answers given by the patient during the telephone interview
- Adverse Event information (based on a telephone interview with the patient)
- Device Deficiency information (based on a telephone interview with the patient)

8.1.4.7 Adverse Events and Device Deficiencies

The investigator has to record any adverse event or device deficiency which occurs during study duration on the corresponding eCRF. The adverse event will be classified according to the seriousness, the relation to the investigational devices and to the procedure. The definition of event classification is described in section 18.

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 devices or as accessory:

- External programming device: BIOTRONIK Renamic or successors
- BIOTRONIK programmer software: Current and subsequent versions
- Remote monitoring tools: BIOTRONIK Smart 3G (or successors)
- Remote monitoring software: HMSC 3 or successors

All devices are used within their intended purpose.

8.1.6 Replacement of subjects

Patients who drop-out before insertion will be replaced. Therefore it is possible that more than 45 patients are enrolled in order to get data from 45 insertions.

8.2 Used devices and comparators

8.2.1 Description of exposure to the investigational device and/or comparator

No comparator is used in this study.

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

- During conduct of the insertion procedure, local anesthesia will be applied around the incision and location of the device pocket.
- Additionally, local and systemic antibiotics might be applied to the patient to prevent wound infection prior and / or after the insertion procedure, according to local clinical practice.

8.2.4 Number of investigational devices to be used and a justification

In this clinical investigation a maximum of 45 individuals will be enrolled (plus potential replacements for drop-outs prior to insertion). To ensure device availability in up to 15 study sites and to account for possible device replacements, about 50 BIOMONITOR III systems will be provided.

For device interrogation up to 15 study sites will be supplied with a Renamic programmer device each, running the study specific programmer software.

8.3 Subjects

8.3.1 Description of patient population

The patient population consists of patients in whom long-term cardiac rhythm monitoring may be 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|CONCEPT.BIOMONITOR III study, patients must fulfill at least one of the following four 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.

Additionally, the following inclusion criteria must be fulfilled:

- Patient is able to understand the nature of study and has provided written informed consent.
- Patient is willing and able to perform all follow up visits at the study site.
- Patient is willing and able to use the CardioMessenger and accepts the BIOTRONIK Home Monitoring concept.

8.3.3 Exclusion criteria

- Patients implanted with ICD or pacemaker.
- Patient is pregnant or breast feeding.
- Patient is less than 18 years old.
- Patient is participating in another interventional clinical investigation according to the definition given below.[1,2]
- Patient´s life-expectancy is less than 6 months.

[1]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.

[2]Patients shall not be enrolled in two interventional clinical investigations at the same time. Enrollment of patients who are already enrolled into an interventional clinical investigation is prohibited by an exclusion criterion. If the patient wants to consent for another study, and the investigator knows this beforehand, the investigator shall ask for an agreement from the sponsor, and if not granted, shall ask the patient not to participate in the second study. If the investigator finds out that the patient has been enrolled into another study, the investigator shall inform the sponsor (see section 9.10.2 "Responsibilities of the investigator"). The sponsor may decide to exclude the patient from the study only if further CIP required procedures offer a risk of a reciprocal effect with the treatment of the other study.

Decisions and deviations have to be discussed upfront (if applicable, during the advisory stakeholder meeting) and documented respectively (e.g. via Note to File and reported as CIP deviation or supporting document "Internal Steering Committee").

8.3.4 Drop-out criteria

8.3.4.1 Exclusion by investigator decision

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 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.

8.3.4.2 Exclusion after failed insertion or explantation

Patients in whom the insertion fails or in whom the study device is explanted shall be excluded after all adverse events are terminated and the corresponding eCRFs have been thoroughly completed.

8.3.4.3 Withdrawal of patient consent

Patients may withdraw their consent for study participation at any time without stating a reason and without any unfavorable consequences. In any case, no further collection of data will occur. If the patient choses to withdraw consent concerning both, study participation as well as the processing of personal data he/she will no longer take part in the study and the data will be anonymized or deleted, so that it is impossible to reconnect the data to the patient's identity.

In case the patient choses to leave the consent for the processing of personal data unaffected, BIOTRONIK will further store, process and analyze the pseudonymized data that was collected prior to withdrawal.

8.3.5 Point of enrollment and study termination

Date of enrollment is the date of signature of the informed consent form.

Date of termination is either the date of the 1-month telephone interview, or – e.g. when no interview was possible - the date of the CardioReport, which is basis for the 1-month Home observation data (see 8.1.4.6).

8.3.6 Timelines

First patient in (FPI):	~ Feb 2019
Last patient in (LPI):	~ May 2019
Enrollment period:	~ 3 months
Last patient out (LPO):	~ Jun 2019
Duration of study participation:	~ 1 month
Finalization of study report	~ Sep 2019

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

9 STUDY PROCEDURES

9.1 Overview

Subsequent to the enrollment and the insertion of the investigational device, one follow-up visit and a Home Monitoring observation one month after the insertion are scheduled. During all study visits designated BIOTRONIK employees who are appropriately trained on the subject matter are allowed to handle programmer data.

The visits and observations should take place within a certain time frame as listed in **Table 2**. This schedule should be followed as closely as possible. 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 respective eCRF.

Table 2: Overview of study procedures

	Enrollment / baseline	Insertion	1–week follow-up -2 days / +1week	1–month Home Monitoring observation, telephone interview
Check inclusion / exclusion criteria	X			
Obtain informed consent	X			
Demographics, medical history, indication	X			
Insertion of BM III and assessment of insertion procedure and tool handling		X		
Interrogate BM III device and provide programmer data		X	X	
Program BM III with indication specific settings		X		
Program periodic subcutaneous ECG (cycle duration 1 day)		X		
Provide CardioMessenger and Remote Assistant, incl. test of Remote Assistant		X		
R-wave amplitude (based on programmer screen)		X		
R-wave amplitude (via HMSC)			X	X
Noise rate (via HMSC)			X	X
Assess P-wave visibility, based on periodic sECGs			X	X
Read-out of BM III data (RAM-dump)			X	
Restart statistics and recordings after read-out of BM III data			X	
Patient interview via telephone				X
Adverse Event and Device Deficiency reporting	X	X	X	X
Fill-in eCRFs	X	X	X	X

9.2 Enrollment / Baseline

Prior to enrollment into the clinical investigation, the investigator will evaluate the eligibility of each patient considering all inclusion and exclusion criteria (see sections 8.3.2 and 8.3.3). The informed consent must be obtained before initiating any study related procedures. The consent process, including discussion of the study related aspects, will be documented in the subject's medical record. After obtaining informed consent, the subject has to be registered in the iMedNet System. After registration, the patient will be assigned a pseudonymized ID code to be used in the study and the patient has to be entered in the patient identification log.

In the enrollment eCRF the following data has to be recorded:

- Version number of the ICF
- Confirmation that patient met all inclusion and none of the exclusion criteria
- Confirmation that the patient dated and signed the patient ICF personally
- 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 should be collected and entered in the baseline evaluation eCRF.

- Date of enrollment / baseline visit
- Demographic characteristics (date of birth, gender, height, weight)
- Details on the ICM indication of the patient
- Medical history of patient

9.3 Insertion visit

The device insertion should be completed within 4 week after informed consent. Otherwise the patients study participation will be terminated.

9.3.1 Device insertion

BIOMONITOR III should be inserted as described in the IFU and in accordance with section 4.7.1.10. The investigator determines the insertion site in accordance with the individual patient characteristics. Time of insertion start and time of final wound closure should be documented on the insertion source data sheet (SDS) (see section 9.3.2).

If the patient consents to a video recording as described in the consent form, the implantation procedure itself is allowed to be videotaped. The patient's face shall not be identifiable in that recording. Recording of the insertion should not delay the insertion procedure or otherwise interfere with the clinical routine.

9.3.2 Procedure after insertion

The following procedures shall be conducted after insertion:

- Interrogate the newly inserted BIOMONITOR III device.
- Freeze, store and print the sECG window and document the R-wave amplitude value on the insertion SDS. In case of varying amplitude labeling, document both, the lowest and the highest amplitude value (Figure 9 and Figure 10).

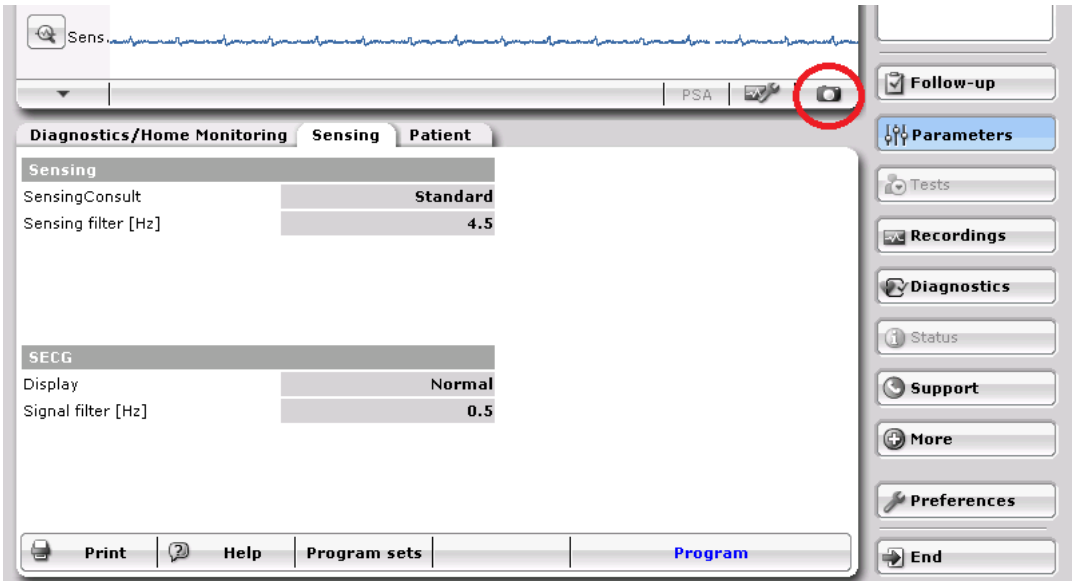


Figure 9: Freeze screen during interrogation

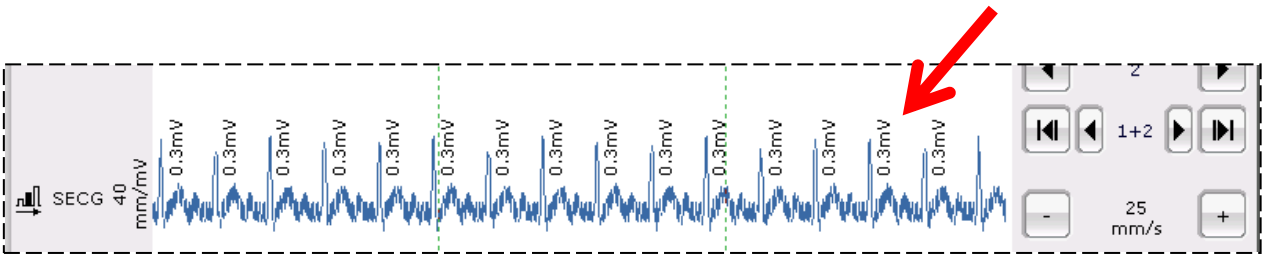


Figure 10: Document R-wave amplitude based on programmer screen or printout

- Program the BIOMONITOR III according to the clinical indication of the patient. Consider using the indication specific program settings (Go to ´Parameters´ – `Program sets´ – `Program consult´, Figure 11)

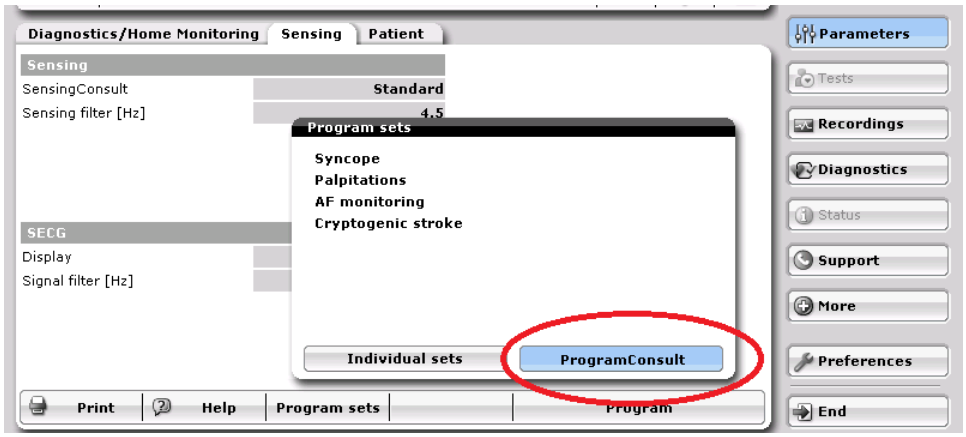


Figure 11: Use `ProgramConsult" for indication specific programming

- Program the Home Monitoring function 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 to the EDC-database (iMedNet) or by using the ReportShare-function (see 4.7.1.11). Alternatively, the PDF file can be send to the study e-mail address (BM3CONCEPT@biotronik.com).
- 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 12.

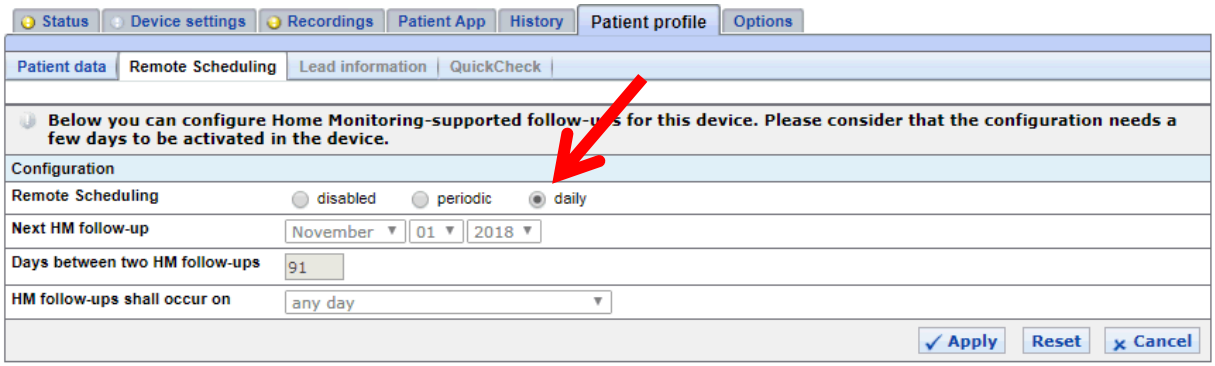


Figure 12: Activate daily periodic sECG recording in HMSC

- Provide the Remote Assistant III to the patient and explain how to use the Remote Assistant III correctly. Let the patient trigger one sECG recording.
- Complete the insertion SDS and enter data in the insertion eCRFs in the iMedNet EDC database.
- Document any adverse event or device deficiency during the procedure by using the respective eCRF. Adhere to the reporting timelines listed in section 18.

9.3.3 Assessment of the insertion procedure

The investigator needs to give details on the insertion procedure and should assess the insertion procedure and tool handling. The following data shall be provided on the insertion SDS and eCRF:

- Time of insertion start
- Time from incision to insertion end
- Time from incision to wound closure
- Insertion site and BIOMONITOR III orientation
- Type of pocket closure
- Usage of anesthesia and antibiotics
- Device repositioning, if applicable
- Assessment of incision tool handling
- Assessment of FIT OneStep insertion tool handling

9.4 1-week follow - up

After 1 week (-2 days / +1 week) following the device insertion, patients return to the investigation site for an in-office assessment of their implanted system. The following procedures shall be conducted:

- Interrogate the BIOMONITOR III device.
- Adjust patient specific program parameters, if applicable. Consider using the indication specific program settings (Go to `Parameters´ – `Program sets´ – `Program consult´).
- Store the electronic procedure data (including final device settings, measurements) of the BIOTRONIK programmer. Provide the programmer data by uploading the PDF-File to the EDC-database (iMedNet) or by using the ReportShare-function. Alternatively, the PDF file can be send to the study e-mail address (BM3CONCEPT@biotronik.com).
- Perform a complete device data read out (i.e. RAM –dump, see 9.7).
- Restart device statistics
- Within the HMSC:

  Inspect the first periodic sECG episode after the day of insertion. In patients with sinus rhythm, evaluate the number of expected and observed P-waves which can be undoubtedly identified.

  Inspect the latest periodic sECG episode which was successfully transmitted to the HMSC. In patients with sinus rhythm, evaluate the number of expected and observed P-waves which can undoubtedly be identified.
- Enter the dates and values in the 1-week follow up SDS. Provide a PDF file export (CardioReport) from the HMSC with the respective episodes and upload the PDF-Files to the EDC-database (iMedNet). Alternatively, the PDF files can be send to the study e-mail address (BM3CONCEPT@biotronik.com).
- Inspect the trend values for sensing amplitude (R-wave amplitude) and noise burden. Values are automatically provided via HMSC, therefore no eCRF entry is necessary.
- Complete the 1-week follow up SDS and enter data in the 1-week eCRFs in the iMedNet EDC database.
- Document any adverse event or device deficiency observed during the follow-up by using the respective eCRF. Adhere to the reporting timelines listed in section 18.

9.5 1-month Home Monitoring observation and telephone interview

One month after the device insertion, the investigator is asked to enter the HMSC and to inspect the daily transmissions of the patient. Additionally, the patient should be contacted via telephone and shall be interviewed. The following procedure shall be conducted:

- Within the HMSC:

  Inspect the periodic sECG episode, which is closest to 30 days after insertion date and which was successfully transmitted to the HMSC. In patients with sinus rhythm, evaluate the number of expected and observed P-waves which can undoubtedly be identified.
- Enter the date and values in the 1-month follow up SDS. Provide a file export (CardioReport) from the HMSC with the respective episode and upload the PDF-File to the EDC-database (iMedNet). Alternatively, the PDF file can be send to the study e-mail address (BM3CONCEPT@biotronik.com).

- Inspect the trend values for sensing amplitude (R-wave amplitude) and noise burden. Values are automatically provided via HMSC, therefore no eCRF entry is necessary.
- Contact the patient via a telephone call and question the patient about any adverse events related to the BIOMONITOR III or the insertion procedure. Ask the patient to answer the questions given on the 1-month follow-up SDS regarding the wearing comfort of the BIOMONITOR III and usability of the Patient APP, if applicable.
- Document any adverse event or device deficiency by using the respective eCRF. Adhere to the reporting timelines listed in section 18.
- Complete the 1-month follow up SDS and enter data in the 1-month eCRFs in the iMedNet EDC database.

9.6 Interim follow-up

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

In case of BIOMONITOR III revision or replacement during study participation the following data shall be entered on the AE-eCRF:

- Reason for revision or replacement
- Revision/replacement procedure information (date of intervention, type of intervention, information about the new implanted devices)
- Insertion position for revised / replaced BIOMONITOR III

In case of BIOMONITOR III explantation during study participation the following data shall be entered on the AE-eCRF:

- Reason for explantation
- Explantation procedure information (date of intervention, type of intervention)
- Information about new device (e.g. pacemaker), if applicable.

Please note that explanted BIOMONITOR III devices must be returned to BIOTRONIK for analysis.

9.7 Device data read out

For the download of the device data read out (RAM-Dump), the following steps are required:

- Connect an USB flash drive to the Renamic with a storage capacity of at least 256 MByte.
- Apply the programming head above BIOMONITOR III.
- Download the data from the BIOMONITOR III memory while the patient is in a reclined position. Select the items as shown in Figure 13. The data transmission can take about 5 minutes. `More" → `BIOMONITOR III´ → `Device Data" → `Read out´
- Please provide the USB flash drive to a BIOTRONIK employee or send the electronic data to the Center for Clinical Research of BIOTRONIK using the study email address BM3CONCEPT@BIOTRONIK.com

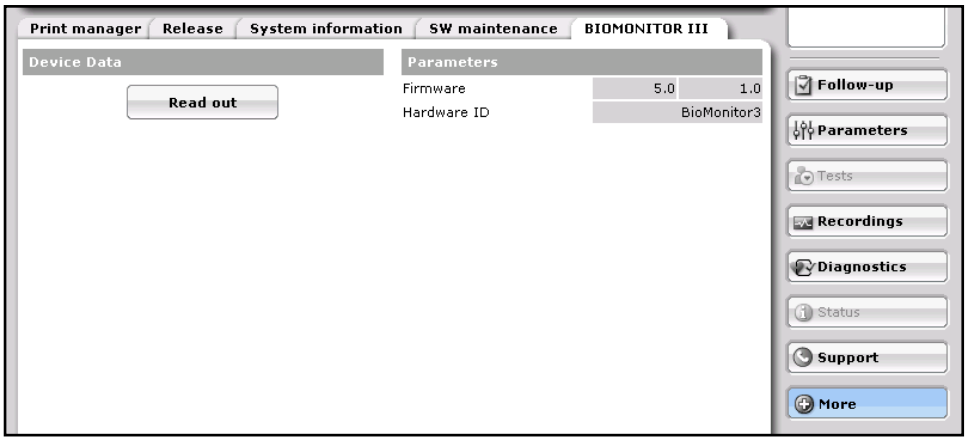


Figure 13: Device data read out

9.8 Termination and post treatment

The study termination eCRF must be completed to determine the end and reason for study termination of the individual patient. The regular termination of the patient is defined as the time when the 1-month Home Monitoring observation and telephone interview is completed. The frequency and elements of routine visits according to standard guidelines for ICM therapy are adequate for all patients after regular study termination.

In the case of patients who do not show up for the scheduled 1-week follow-up, all efforts should be made to contact them and complete the required checks, even if this would be far out of the planned schedule. Equally, all efforts should be made to contact the patient for the 1-month follow-up to assure that no adverse events will remain unnoticed. It should be kept in mind that the study device has no market approval and is implanted only under the condition that the patient is followed in this study.

Follow-up of subjects which have withdrawn consent is covered in section 8.3.5.1.

9.9 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.

9.10 Responsibilities

9.10.1 Responsibilities of the sponsor

The sponsor of the BIO|CONCEPT.BIOMONITOR III study is:

BIOTRONIK Australia Pty. Ltd.
Level 4, Building 2
20 Bridge St

Pymble NSW 2074
Australia

Comprehensive responsibilities regarding study conduct and management are delegated to:

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

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

In addition, the sponsor and delegates are 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.
- Responsibility for all payments and financial coverage of the study, including patient travel reimbursement.
- Supervision of study conduct according to the legal regulatory requirements and the requirements of the CIP.
- Fulfill reporting duties of the sponsor to the ethic 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.

9.10.1.1 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 ethic 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 project associates, data assistants, data base managers).

In case of questions concerning the clinical investigation plan, used medical devices and regulatory requirements, the investigator should contact the clinical project manager.

9.10.1.2 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.
- Data management.

9.10.1.3 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.

9.10.1.4 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.

9.10.2 Responsibilities of the investigators

9.10.2.1 Coordinating Investigator

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

A/Prof Justin Mariani
The Alfred Hospital
Department of Cardiology
55 Commercial Road
Melbourne VIC 3004

The responsibilities of the Coordinating Investigator 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 Coordinating Investigator has the same rights and duties as other principal investigators.

9.10.2.2 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.

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 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 system 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 the clinical investigation plan, applicable laws, local regulations and any conditions of approval imposed by the reviewing 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 conducts the clinical investigation in accordance with the CIP, The Declaration of Helsinki, ISO 14155, and applicable 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 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 applicable 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|CONCEPT.BIOMONITOR III study is designed as an open-label, prospective, non-randomized, multicenter one-armed, international study.

For continuous variables, descriptive statistics (mean, median, standard deviation, first and third quartile, minimum and maximum) will be calculated. For categorical variables absolute and relative frequencies (based on the number of non-missing data) will be calculated.

For selected variables two-sided 95% confidence intervals for the respective parameters will be given.

11.2 Sample size

Since no hypothesis will be assessed, no formal sample size calculation based on standard statistical methods can be done.

Instead, the sample size of this study has been deduced following the method proposed by Viechtbauer et al.[57]. A sample size of 45 patients would allow with 95% confidence to observe at least one event of a certain type of events if this type of events would occur with 15% probability in the respective population.

This is not to implicate that a rate of 15% of a certain type of events is expected; it merely means that if unforseen risks existed at such a high rate, one might be 95% confident to observe at least one such event in the study and measures could be taken before market introduction.

11.3 Level of significance and the power of the study

A p-value of less than 0.05 will be considered to indicate statistical significance for any comparison. Since no hypotheses are specified, no power can be defined.

11.4 Expected drop-out rate

The drop-out rate is expected to be < 10 %.

11.5 Pass/fail criteria

Not applicable.

11.6 Provision for an interim analysis

An interim analysis is planned in June 2019. All available data will be analyzed to support the management decision regarding product launch of the BIOMONITOR III. Additionally, it could be necessary to run preliminary ad hoc analyses. If so, no bias is expected because no hypotheses are defined.

11.7 Termination criteria

Because of the small number of patients and explorative character of the clinical investigation there are no termination criteria based on statistical considerations.

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 database by the investigators via the iMedNet electronic data capture system (MedNet Solutions, USA). Exports from the database will be analyzed with common validated statistical software packages (e.g. SAS or R).

11.11 Handling of missing, unused and spurious data

Missing data will not be imputed.

Spurious data will be clarified via the query management, i.e. corrected after approval of an investigator. Remaining outliers will be identified during the review of the data before data base closure. In case of a clear evidence of a measurement error, the Statistical Analysis Plan will be updated in order to avoid any bias. Spurious data, which were not clarified by the query process before database closure, will be indicated. If appropriate, analyses will be performed both with /without such data.

11.12 Exclusion of data from confirmatory data analysis

In the following cases, data are to be excluded from analysis or prevented from inclusion into analysis:

- No data is allowed to be collected and included in the absence of a documented consent
- After withdrawal of consent, collected data may only be stored, processed and analyzed if the patient left the consent of processing of personal data unaffected. Details are provided in the Statistical Analysis Plan.

11.13 Minimum and maximum number of patients per site

The number of subjects attended by each study investigator shall not exceed 5, because it is most relevant for the study to have an opinion on the usability of the insertion tool from as many as possible different physicians. Exemptions will be communicated in written form in case enrollment is too slow.

Study centers may enroll more than 5 patients if a second or even a third investigator performs the insertion procedure.

12 DATA MANAGEMENT

The established Clinical Data Management System (CDMS) is `iMedNet" from the vendor MedNet Solutions, Inc. As a pure internet-based application that is used with the current versions of most internet browsers, there is no specific local software needed for support (cloud based `Software as a Service" SaaS). iMedNet supports industry standards (FDA 21CFR11, HIPAA and Safe Harbor).

12.1 Data protection

According to corresponding national laws the patient (or his or her legal representative) 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, and, if necessary, to responsible Ethic Committee (EC) and Competent Authority (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 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|CONCEPT.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 for 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 11 and HIPAA).

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 in the Monitoring Plan or at the respective section of the CIP.

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 content are exported and stored electronically for at least 15 years on the archive server.

At the end of this period, requirements from laws and other regulations will be reconsidered in order to decide whether the retention period must be extended or data must be deleted.

All relevant study related documents have to be stored in the Investigator 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 principal 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 an amendment agreement form if no new CIP 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 deviation log BIOTRONIK personnel / third parties, 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.

In order to comply with guidance from the Australian government agency, the National Health and Medical Research Council (NHMRC), it needs to be ensured that serious breaches of GCP are reported within 7 calendar days to the respective EC.

A serious breach is a deviation from the CIP which is likely to affect to a significant degree

- the safety or rights of a trial participant, or
- the reliability and robustness of the data generated in the clinical investigation.

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 or in the corresponding deviation log BIOTRONIK personnel / third parties, 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 investigational devices which are not approved for an overall market release and are labeled `for clinical investigation only´ 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´.

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 sponsor. 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 of the informed consent discussion as well as date 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.

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) iMedNet. 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.

*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, implantation, installation, or operation, or any malfunctioning of the investigational device and any event resulting from use error or from unintentional misuse of the investigational device.

*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 adverse event to the investigational device or procedures and the sponsor will review the investigators 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 reasonably explained by another cause, but additional information may be obtained.

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

The investigators will distinguish between the adverse events related to the investigational device and those related to the device procedures (any procedure specific to the investigational device). Procedure related events refers 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. replacement after device migration), 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 patients also in the absence of investigational device use or 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 a SADE,

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

the DD is classified as an DD with an 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 documenting the cause of death, 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
- 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 is considered serious.

*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 of the BIOMONITOR III and are therefore assessed as procedure related adverse device effects. They are listed in **Table 3**as sorted by their incidence rates. For all references used for this chapter, refer to the list at the end of this section.

Table 3: 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, 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 CRF pages provided within the CDMS. The indicated timelines for reporting of initial cases and possible update reports shall be strictly followed.

All Serious Adverse Events (SAE) and Serious Adverse Device Effects (SADEs) 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 (S)A(D)Es 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. SADEs ongoing SADEs at the subjects regular study termination should be followed up for further four weeks or until resolution whatever comes first. Ongoing SADEs related to the investigational device will be followed until termination of the study if not resolved before.

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 the 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 EC, 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 a 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 the Ethic 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 a SADE on a regular basis. As a proposal, regular listings may be provided monthly 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 4**.

Table 4 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.

Please note that 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: +49 (0) 30 68905-2200.

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 8.3.2 and 8.3.3). Therefore no provisions for vulnerable patients have to be arranged.

20 SUSPENSION

20.1 Criteria and procedures

Suspension or premature study termination at an investigational site 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 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 (S)A(D)E 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'. SADEs ongoing at the subjects regular study termination should be followed up for further four weeks or until resolution whatever comes first.

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 furthers 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 one 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

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, the membership on committees or boards, 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 implanted investigational device
- 1 point for each patient, with complete and 100% compliant data set until regular study termination according to clinical investigational plan
- -1 point for each scheduled follow- up visit that is outside of the defined timeline provided by this CIP or that remain unreported
- -1 point for each Serious-Adverse-(Device)-Event not reported within the timeline provided by this CIP

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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