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Clinical Investigation Plan

for the

BIO|CONCEPT.ECG-Library

Collection of ECG signals from various patient groups for the development of algorithms for sensing and detection of rhythm anomalies

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

A current list of the principal investigators at each investigational site, the address details for each investigational site, the emergency contact details for the principal investigator at each site and a detailed list of sponsor contacts are filed in the Central File.

Signature of the Principal Investigator

Name: _____

Institution: _____

_____

Street: _____

ZIP code/ City: _____

Country: _____

I have read this Clinical Investigation Plan (CIP) and agree to adhere to the requirements described in this study protocol.

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

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

_____ _____

City, date Signature of Principal Investigator

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1 LIST OF ABBREVIATIONS

ADE	Adverse Device Effect
AE	Adverse Event
AF	Atrial Fibrillation
AVNRT	Atrioventricular Nodal Reentrant Tachycardia
AVRT	Atrioventricular Reentrant Tachycardia
BMT	Body Motion Test
CA	Competent Authority
CDMS	Clinical Data Management System
CF	Compact Flash
CIP	Clinical Investigation Plan
CRA	Clinical Research Associate
DLO	Daily Living Observation
EC	Ethic Committee
ECG	Electrocardiogram
CRF	electronic Case Report Forms
EPS	Electrophysiology Study
FDA	US Food and Drug Administration
FPI	First Patient In
ICD	Implantable Cardioverter Defibrillator
ICF	Informed Consent Form
ID	Identification Number
ILR	Implantable Loop Recorder
ISO14155	International Organization for Standardization, norm no. 14155
LBBB	Left Bundle Branch Block
LPI	Last Patient In
LPO	Last Patient Out
NYHA	New York Heart Association
PI	Principal Investigator
RBBB	Right Bundle Branch Block
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
VES	Ventricular Extrasystole
VT	Ventricular Tachycardia
WPW	Wolff-Parkinson-White

2 SYNOPSIS

Title	Collection of ECG signals from various patient groups for the development of algorithms for sensing and detection of rhythm anomalies
Patient population	Patients from the investigator's general collective and with different forms of diagnosed arrhythmias and/or specific ECG characteristics from heart diseases as listed in the inclusion criteria.
Design	Prospective, multicenter, non-randomized, interventional
Objectives	Collect data from surface ECGs by using Holter ECG recordings from patients with different forms of diagnosed arrhythmias and/or specific ECG characteristics from heart diseases to support the development of new sensing and detection algorithms for implants.
Endpoints	Number of successful ECG recordings per condition
Additional Data of Interest	• Demographic data, medical history, ECG diagnosis • Adverse Events related to the study procedure • Optional: chest x-ray, only if available and part of a procedure prior to enrollment
Inclusion criteria	• Patient is able to understand the nature of the study and willing to provide written informed consent • Patient is willing and able to attend Holter ECG procedure following a visit • History of at least one of the following conditions (established via ECG prior to enrollment): (A) Patient with pacemaker/ICD and 1. Ventricular stimulation > 30 % or (B) Patient either without pacemaker/ICD, or with pacemaker/ICD but without significant atrial and ventricular stimulation, and at least one of the following: 2. Frequent Ventricular Extrasystoles (VES) (incl. Bigeminus) or 3. Atrioventricular Reentrant Tachycardia (AVRT)/ Wolff-Parkinson-White (WPW) syndrome or 4. Atrioventricular Nodal Reentrant Tachycardia (AVNRT) or 5. Sinus Tachycardia at rest or 6. Atrial Flutter or 7. Any form of Ventricular Tachycardia (VT) or 8. Silent/paroxysmal/persistent/permanent AF or 9. Brugada syndrome or 10. Long QT syndrome or 11. Right Bundle Branch Block (RBBB) or

12. Left Bundle Branch Block (LBBB) or
13. Myocardial Ischemia/Acute Myocardial Infarction or
14. Other abnormal QRS(T) complex, ST segment or T-wave morphology, i.e. any other
    - QRS anomaly
    - ST segment elevation
    - ST segment depression
    - T wave changes

Exclusion criteria	• Any condition which precludes the patient's ability to comply with the study requirements • Known allergy to patch electrodes • Pregnant or breast feeding • Less than 18 years old • Participation in another interventional clinical investigation
Study duration	Approx. January 2020 – November 2020 (approx. 11 months)
Sample size	100 patients
Investigational sites	Approx. 5
Number of follow-ups per patient	• One investigational procedure scheduled, in general in conjunction to a routine follow-up. • In case of participation in the Daily Living Observation: One visit for the return of the Holter ECG device.
Follow-up scheme	Scheduling of patient enrollment and data collection, including Holter ECG recording, is left to the investigator's discretion. It is expected that in most cases this will happen in conjunction to a routine follow-up. Study procedures: • Enrollment • Holter ECG Recording (procedure depending on inclusion criteria): – 3-Patch Holter ECG Recording: Holter Recording during Electrophysiological Studies (EPS) followed by 24-hour Holter ECG Recording with Daily Living Observation (optional) – 10-Patch Holter ECG Recording: Holter ECG recording during Body Motion Test followed by 24-hour Holter ECG Recording with Daily Living Observation • Termination
Sponsor	BIOTRONIK SE & Co. KG Woermannkehre 1 D-12359 Berlin

3 INTRODUCTION

In cardiology, a variety of biomedical implants uses Electrocardiograms (ECGs) from various types of electrodes for different diagnostic and therapeutic purposes. For subcutaneous ECG recorders and subcutaneous implantable cardioverter defibrillators (ICDs), placement of their subcutaneous electrodes poses a special technical challenge, since an unreliable signal detection limits the performance of these implants [1][2].

For all such devices, signal quality is highly dependent on the positioning and type of electrode. It is assumed that ECGs obtained from surface patch electrodes are similar to those from subcutaneous electrodes [3].

In this study, data gathered from various patient groups with heart rhythm disorders and ECG anomalies will be collected and used to improve ECG evaluation and specific algorithms for medical devices and implants, such as subcutaneous ICDs or implantable loop recorders.

4 INVESTIGATIONAL DEVICE

4.1 Summary description of the device and its intended purpose

This study will not investigate a medical device or medicinal product. This exploratory investigation aims to collect clinical real-life data of different heart conditions which can be observed via Holter ECG recordings.

Therefore no investigational device is defined.

4.2 Intended patient population and indications

According to the exploratory character of the study, the patient population will be chosen from the investigator's general collective and with different forms of diagnosed arrhythmias and/or specific ECG characteristics from heart diseases as listed in the inclusion criteria (section 8.3.2). This can include, but is not limited to:

- Patients undergoing an electrophysiological study (EPS)
- Patients attending a routine follow-up for their cardiac disease
- Patients attending a device follow-up
- Patients indicated for a pacemaker/ICD implant or exchange
- Patients indicated for the implantation of an implantable loop recorder (ILR)

4.3 Summary of training and experience needs

All (co-)investigators must have a record of adequate research training and experience. Training on ISO 14155 and/or several years of experience in conducting clinical trials are generally required. All participating site staff will be trained by the sponsor or its representative on the requirements of this Clinical Investigation Plan (CIP).

The investigator or his designated representative must be familiar with the use of the Holter ECG equipment and in conducting Holter ECG recordings. For the placement of the ECG patch electrodes, the set-up, and the conduct of the Holter ECG recording, instructions will be given in section 9 as well as supporting documents will be provided by the sponsor.

5 JUSTIFICATION FOR THE DESIGN OF THE CLINICAL INVESTIGATION

5.1 Pre-clinical data and Clinical data

Since the aim of this study is to obtain real-life information on ECGs from a variety of different arrhythmias and heart conditions via surface ECG, this study set-up is not experimental and does not require clinical testing.

5.2 Justification

Subcutaneous ECG recorders and electrodes are implanted for diagnostic monitoring purposes and - in case of electrodes - for treatment of occurring arrhythmias. However, unreliable signal detection limits the success of such implants. For the development of appropriate detection and sensing algorithms in such devices, a prospective and non-randomized design was chosen to acquire ECG examples from patient groups with different cardiac indications. In addition, a multi-centric approach was chosen to avoid investigator- or site-related bias.

In previous studies, investigations were mainly conducted to collect ECGs to evaluate the placement of electrode specific for implantable loop recorders; however, for the development of additional detection and sensing algorithms for electrodes, ECGs from additional electrode placements are required.

Since ECGs vary in the different forms of cardiac diseases, patients exhibiting different forms of arrhythmias and/or heart diseases need to be enrolled. Patients will be screened prior to enrollment by the study staff for their assignment to one of these groups. If a patient can be assigned to more than one subgroup, the resulting ECG will be evaluated internally by the sponsor and allocated to one or more subgroups.

6 RISKS AND BENEFITS OF THE DEVICE AND CLINICAL INVESTIGATION

6.1 Anticipated clinical benefits

The study is designed to gain real life clinical data from various patient groups who suffer from different arrhythmias and/or heart diseases. Data gathered in this investigation will be used to further the development and improvement of algorithms required for the sensing and detection of such arrhythmias. Future patient populations might benefit from the diagnostics and therapeutic devices developed by the use of the study data.

The subject participating in the study may benefit from its study participation in that the study-specific ECG recording might reveal a so far unknown medical condition.

6.2 Anticipated risks

6.2.1 Anticipated adverse device effects

Since no investigational device will be used in the study, no adverse device effects are anticipated during the study.

6.2.2 Residual risks associated with the device

Since the study does not evaluate an investigational device, no such residual risk can be implied.

6.2.3 Risk associated with participation in the study

There is a potential risk for the subject to develop skin reactions in response to the application of multiple surface ECG electrodes, such as irritation or inflammation. In addition, the subject may experience a discomfort caused by wearing the ECG patches, the Holter ECG device, or the cabling of the device. Discomfort or dizziness may also occur during the study specific Body Motion Test (BMT) during the recordings.

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

No other risks are anticipated with the participation in the study.

6.3 Steps to control or mitigate the risks

Risks associated with a Holter ECG recording which are mentioned above, as well as in section 18.3, are minimized through the utilization of hypo-allergenic patch electrodes, compliance with the user 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.

Data protection laws, in particular the Regulation (EU) 2016/679 of the European Parliament and of the Council and its Corrigendum dated May 23, 2018 as well its respective national versions must be followed where applicable. Thus, patient names may not be used as patient IDs. Non-pseudonymized data inadvertently sent to the sponsor will be handled upon discovery according to BIOTRONIK's internal processes to ensure that only pseudonymized documents are available at and used by the sponsor. Access to the clinical data management system (CDMS) is restricted by secured internet platforms using user IDs and passwords. Further details on the risk mitigation regarding the CDMS are outlined in the data management plan of the study. Nevertheless, a residual risk remains.

6.4 Risk-to-benefit rationale

The patient may directly benefit from possible findings or observations, which could prevent potential unobserved risks. Possible risks associated with the Holter ECG procedure and the Body Motion Test are temporary in nature and in general not considered serious.

The main long term clinical benefit will derive from substantial improvements of sensing and detection algorithms, thus ultimately affecting patient safety by developing new leads and devices.

Therefore it can be concluded that the overall benefits outweigh the risks.

7 OBJECTIVES AND HYPOTHESES

7.1 Objectives

The objective is to build a library of surface ECG signals from patient groups with different forms of diagnosed arrhythmias and/or specific ECG characteristics from heart diseases. The signals will be used to support the development and improvement of algorithms for the accurate detection and sensing of rhythm anomalies.

7.2 Endpoints and hypotheses

As described in section 11.2, the number of successful ECGs per condition stated in the inclusion criteria (section 8.3.2) was chosen as an endpoint, whereat each condition shall be included at least six times and at most ten times; with the exception of 'Any form of Ventricular Tachycardia (VT)' being included at least twelve times or more.

There are no predefined hypotheses.

7.3 Further data of interest

- Demographic data, medical history, ECG diagnosis
- Adverse Events related to the study procedure
- Optional: chest x-ray, only if already available and part of a procedure (e.g. implantation) that occurred prior to enrollment

8 DESIGN OF THE CLINICAL INVESTIGATION

8.1 General considerations

8.1.1 Type of clinical investigation

The clinical investigation is a prospective, multicenter, non-randomized, interventional data collection with no additional follow-up procedures.

8.1.2 Measures taken to minimize or avoid bias

A multicenter approach was chosen to reduce bias that might arise from site or investigator specific methods and customs.

8.1.3 Methods

8.1.3.1 CRFs

All procedures that are recorded within the study are described in section 9 and are documented on the corresponding electronic case report forms (CRFs). The investigator is required to use an electronic signature to approve the content of the data reported in the CRFs. BIOTRONIK will monitor the content of the CRFs as described in section 10. Data from the following procedures will be collected:

- Enrollment/Baseline
- Holter ECG recording, including participation in the Body Motion Test (BMT) and Daily Living Observation (DLO)
- Termination

The following events can be documented at any time:

- Adverse Event (AE)

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

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

Patients have to consent to the use of their medical data in the patient file by signing the informed consent form.

8.1.3.2 Source Data verification

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

- Patient is able to understand the nature of study and willing to provide written informed consent
- Patient is willing and able to attend the Holter ECG recording
- Any condition which precludes the patient's ability to comply with the study requirements
- Known allergy to patch electrodes
- Pregnant or breast feeding
- Participation in another interventional clinical investigation according to the definition given below.

The following Source data sheet (SDS) is recommended to be used:

- Holter ECG recording

8.1.3.3 Allocation of patients to a subgroup by the sponsor

As stated in section 7.2, at least 6 but no more than 10 patients shall be included for each subgroup which defined in the inclusion criteria (section 8.3.2), the exception being 'Any form of Ventricular Tachycardia (VT)' which shall be included at least 10 times or more.

A first allocation of the patient to one or more subgroups will be done by the investigator by completing the enrollment CRF.

A subsequent allocation to a single subgroup will be done internally after the evaluation of the ECG recording by the sponsor's research and development department. After reaching the desired number in one of the subgroups, the sponsor will announce its closure to the participating investigators and data entry will be restricted for patients who are allocated only to this single subgroup.

8.1.4 Replacement of subjects

During the course of the study, patients who drop out prior to or during the Holter ECG recording can be replaced as long as the enrollment phase has not been closed by the sponsor. Patients can also be replaced if they prematurely terminate the Holter ECG recording without documentation of the intended ECG pattern or if the recording cannot be evaluated due to quality issues. Patients in whom the expected ECG-pattern could not be recorded during the course of their regular study participation (e.g. patients with paroxysmal AF) will not be replaced.

Due to replacements, the total number of enrolled patients might exceed the planned sample size.

8.2 Used devices

8.2.1 List of any other medical device to be used during the investigation

The following equipment is used during the study to collect data:

- Holter ECG: Lifecard CF Holter device with 3-patch interface (Spacelabs Healthcare)
  Lifecard CF Holter device with 10-patch interface (Spacelabs Healthcare)
  Compact Flash Card, 256 MB (Spacelabs Healthcare)
- Software: Pathfinder®, Sentinel® (Spacelabs Healthcare)

8.2.2 Number of investigational devices to be used and a justification

Not applicable.

8.3 Subjects

8.3.1 Description of patient population

Data will be collected from patients with cardiac arrhythmias.

8.3.2 Inclusion criteria

- Patient is able to understand the nature of the study and willing to provide written informed consent.
- Patient is willing and able to attend Holter ECG procedure following a visit
- History of at least one of the following conditions (established via ECG prior to enrollment):

  (A) Patient with pacemaker/ICD and

1. Ventricular stimulation > 30 % or

(B) Patient either without pacemaker/ICD or with pacemaker/ICD, but without significant atrial and ventricular stimulation and at least one of the following:

2. Frequent Ventricular Extrasystoles (VES) (incl. Bigeminus) or
3. Atrioventricular Reentrant Tachycardia (AVRT)/Wolff-Parkinson-White (WPW) syndrome or
4. Atrioventricular Nodal Reentrant Tachycardia (AVNRT) or
5. Sinus Tachycardia at rest or
6. Atrial Flutter or
7. Any form of Ventricular Tachycardia (VT) or
8. Silent/Paroxysmal/persistent/permanent AF or
9. Brugada syndrome or
10. Long QT syndrome or
11. Right Bundle Branch Block (RBBB) or
12. Left Bundle Branch Block (LBBB) or
13. Myocardial Ischemia/Acute Myocardial Infarction or
14. Other abnormal QRS(T) complex, ST segment or T-wave morphology, i.e. any other
    - QRS anomaly
    - ST segment elevation
    - ST segment depression
    - T wave changes

8.3.3 Exclusion criteria

- Any condition which precludes the patient's ability to comply with the study requirements.
- Known allergy to patch electrodes.
- Pregnant or breast feeding.
- Less than 18 years old.
- Participation in another interventional clinical investigation according to the definition given below.[1,2]

[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 Drop-out criteria according to protocol

The investigator shall prematurely terminate a patient's study participation due to the following reasons:

- Patient is unable or unwilling to proceed with the Holter ECG recording due to discomfort when wearing the electrodes.
- Patient is unable or unwilling to proceed with the Holter ECG recording due to discomfort or dizziness during the Body Motion Test.
- Holter ECG recording does not take place for any reasons within 14 days after enrollment.

8.3.4.2 Withdrawal of patient consent

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

8.3.5 Point of enrollment and study termination

The point of enrollment is defined as the time of signature of the informed consent form by the patient. Study related procedures, documentation and collection/following of adverse events will start from this time on.

The patient's study participation ends regularly at the moment when the last study procedure according to protocol has been completed.

The point of non-regular study termination can be the following:

- Date of withdrawal of consent
- Date of patient death
- If patient is a drop-out, the date of last patient related patient contact.

Study related procedures and data collection must end at the day of study termination.

8.3.6 Timelines

First patient in (FPI):	~ Jan 2019
Last patient in (LPI):	~ Oct 2020
Enrollment period:	~ 10 months
Last patient out (LPO):	~ Nov 2020
Duration of study participation:	up to 30 days, with up to 2 days active study participation
Finalization of study report	~ Mar 2021

All timelines are subject to change without requiring protocol amendments.

9 STUDY PROCEDURES

9.1 Overview

The following study related procedures (Table 9-1) apply and have to be documented in the respective electronic case report form (CRF) for each patient enrolled.

Table 9-1: Overview of study procedures.

Investigations	Enrollment/ Baseline	ECG Recording (0 to 14 days)		Termination
		3-Patch (EPS)	10-Patch (non-EPS)	
Patient informed consent	x			
Demographic data	x			
NYHA class	x			
ECG history prior to enrollment	x			
Medical history	x			
ECG during EPS		x		
Body Motion Test			x	
Daily Living Observation (24-hour ECG)		(x)	x	
Patient diary		(x)[1]	x	
Return of Holter ECG device				x
Adverse event reporting	x	x	x	x
CRF completion	x	x	x	x

EPS = electrophysiological study

(x) = optional, (x)[1] = optional, only during 24 h ECG, x = if applicable

9.2 Enrollment/Baseline visit

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

After a subject has been enrolled, the following data have to be collected and entered in the respective CRF:

- Date of baseline assessment
- Demographic data

- Medical history (for NYHA class and ECG diagnostics: within three months prior to enrollment)

Note: Medication shall be documented in the context of adverse events.

During the baseline visit, the study staff may discuss with the patient their options for scheduling the different Holter ECG applications:

For patients undergoing an EPS procedure, the Holter ECG will be done in conjunction to the EPS; however the patient has the option either to deny the Daily Living Observation, to continue directly after the EPS procedure (either at home or during his/her hospitalization), or to participate at a later point in time (up to 14 days after the EPS procedure).

For patients participating in the Body Motion Test ('non EPS candidates'), the Holter ECG can be done in conjunction with a routine follow-up or scheduled for a later point in time (up to 14 days after enrollment). After completion of the Body Motion Test, the patient shall be asked whether he/she wants to continue with the Daily Living Observation right after the Body Motion Test or at a later point in time (up to 14 days after the Body Motion Test).

9.3 Holter ECG applications

EPS candidates get a Holter ECG with a 3-patch electrode interface (section 9.3.1). Typical EPS candidates may be patients from the following inclusion groups (compared with inclusion criteria, section 8.3.2):

- (2) Frequent Ventricular Extrasystoles (VES) (incl. Bigeminus)
- (3) Atrioventricular Reentrant Tachycardia (AVRT)/Wolff-Parkinson-White (WPW) syndrome
- (4) Atrioventricular Nodal Reentrant Tachycardia (AVNRT)
- (6) Atrial Flutter
- (7) Any form of Ventricular Tachycardia (VT)
- (9) Silent/paroxysmal/persistent permanent AF
- (14) Other abnormal QRS(T) complex, ST segment or T-wave morphology

Non-EPS candidates get a Holter ECG with a 10-patch electrode interface (section 9.3.2). Typical non-EPS candidates may be patients attending a routine follow-up for their cardiac disease, patients attending a device follow-up or being indicated for implantation or exchange of an ICD or pacemaker. They may be from the following inclusion groups (compared with inclusion criteria, section 8.3.2):

- (1) Patient with pacemaker/ICD and ventricular stimulation > 30 %
- (5) Patient with frequent Sinus Tachycardia at rest
- (9) Patient with Brugada syndrome
- (10) Patient with Long QT syndrome
- (11) Patient with Right Bundle Branch Block (RBBB)
- (12) Patient with Left Bundle Branch Block (LBBB)
- (13) Myocardial Ischemia/Acute Myocardial Infarction
- (15) Other abnormal QRS(T) complex, ST segment or T-wave morphology

However, the decision on whether a patient is included as an EPS candidate or non-EPS candidate is at the physician's discretion.

9.3.1 Holter ECG with 3-patch electrode interface for EPS candidates

If the patient undergoes an EPS procedure, the Holter ECG recording will be done using a 3-patch electrode interface. The ECG patch electrodes will be placed as shown in Figure 9-1. The placement and exact location of each electrode are described detailed in Table 9-2. It is assumed that a standard 12-lead ECG measurement (as indicated in Figure 9-1) is additionally applied.

In this scenario, no extra EPS protocol is planned for the patient, but an ECG is recorded for the whole duration of the EPS after initializing the Holter ECG recording.

At the physician's discretion, additionally, a 24-hour Daily Living Observation (DLO) as described in section 9.3.5 can be done. This test might be performed using the same Holter ECG device with the already applied 3-patch electrode interface. The recording might be in addition to a standard 12-lead ECG measurement for out-of-study purposes within the scope of the routine EPS.

Holter ECG setup tasks must be performed by the study staff according to section 9.3.3. After initialization of the Holter device, the recording shall run continuously throughout the whole EPS procedure unless there are compelling medical reasons for interruption.

There is no extra study-related EPS protocol for the patient and thus there are no supervised activities during EPS.

After execution of the protocol(s), i.e. after EPS procedures or after the 24-hour ECG recording (DLO), respectively, the patient gets the Holter recording stopped (by removing the CF card from the Holter device) and the equipment removed.

Additional documentation will be provided including more details on Holter ECG application.

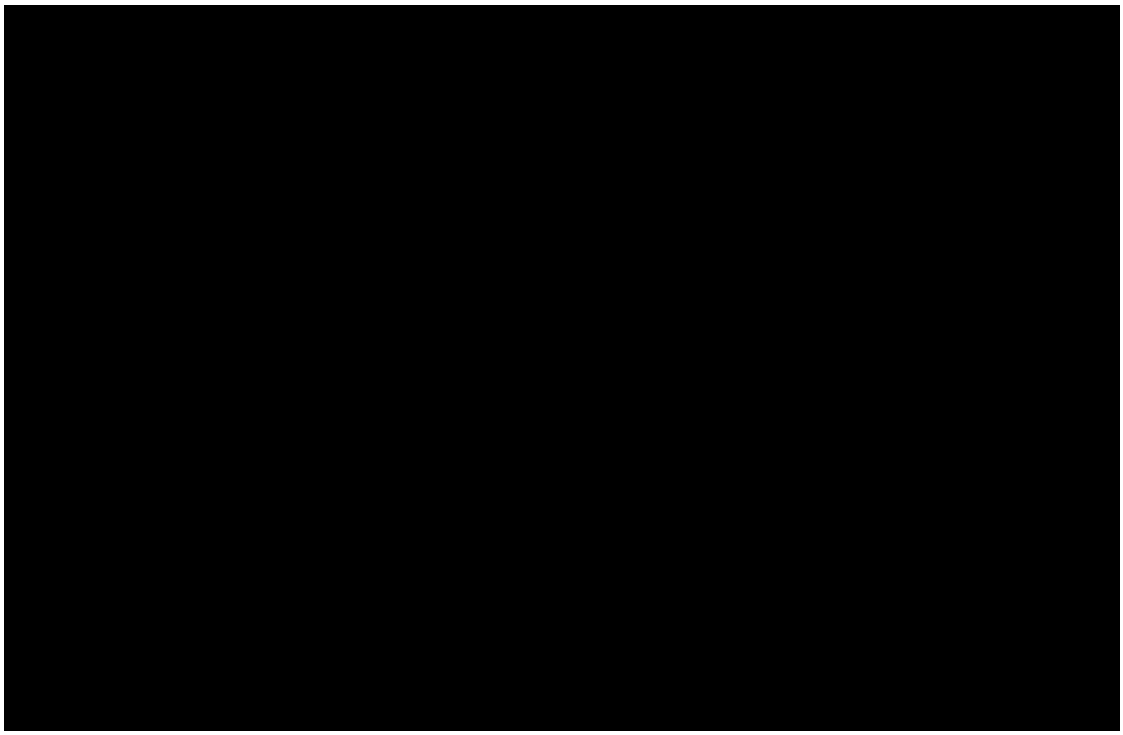


Figure 9-1: Position of the three ECG electrodes

Table 9-2: Description of electrode placement for the 3-patch Holter ECG during an EPS.

[redacted]

9.3.2 Holter ECG with 10-patch electrode interface for non-EPS candidates

For patients without EPS procedure, there is a protocol called Body Motion Test (BMT) (section 9.3.4) where various body positions and activities shall be performed by the patient after initialization of the Holter ECG recording.

For those patients, the Holter ECG recording will be done using a 10-patch electrode interface. The ECG patch electrodes will be placed as shown in Figure 9-2. The placement and exact location of each electrode are described detailed in Table 9-3.

In addition, a 24-hour Daily Living Observation (DLO) shall be performed using the same Holter ECG device with the already applied 10-patch electrode interface.

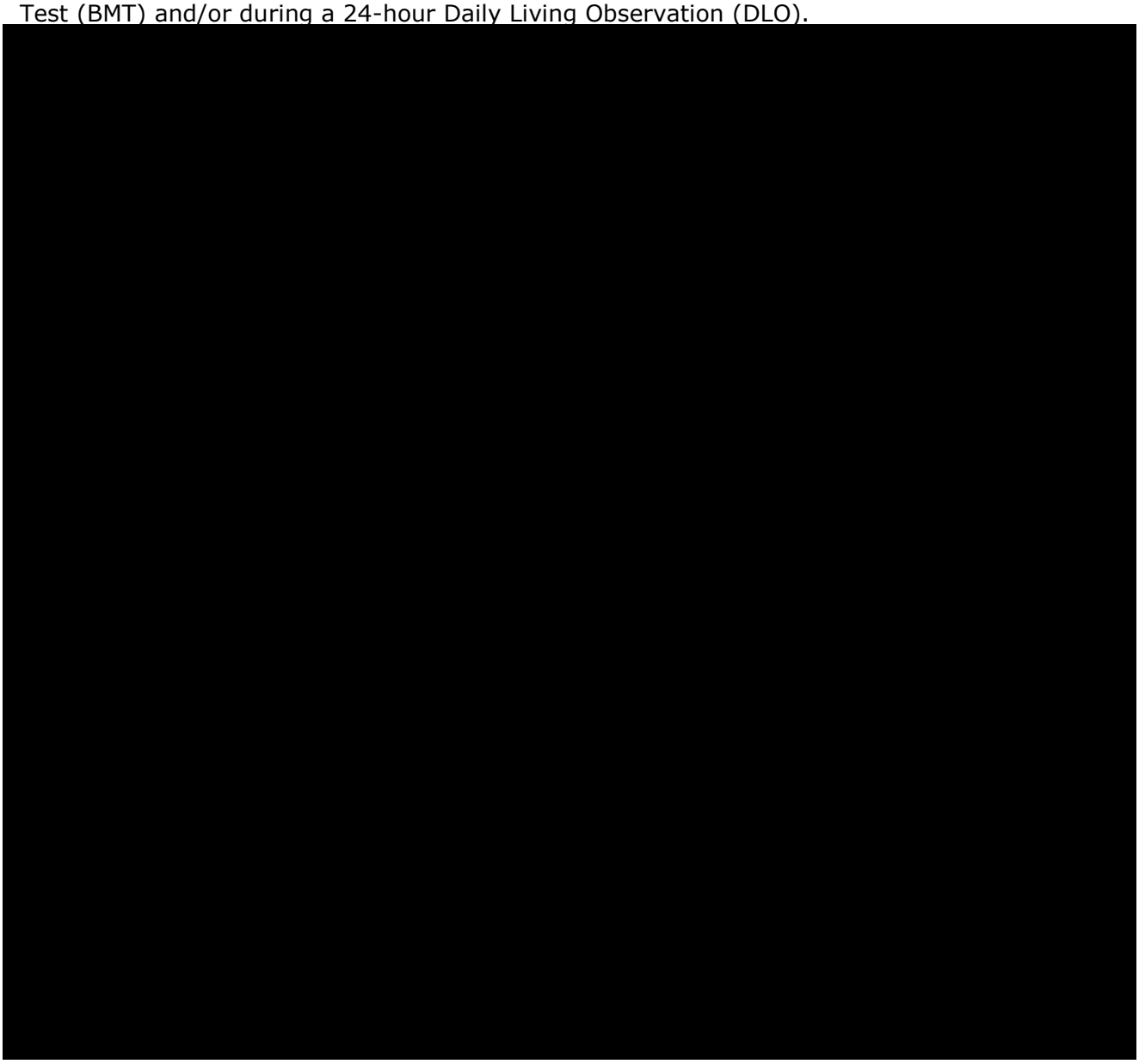
After execution of the protocols, i.e. after the 24-hour ECG recording (DLO), the patient gets the Holter recording stopped (by removing the CF card from the Holter device) and the equipment removed.

Additional documentation will be provided including more details on Holter ECG application.

[redacted]

Figure 9-2: Position of the ten ECG electrodes [redacted]

Table 9-3: Description of electrode placement for the 10-patch Holter ECG during Body Motion Test (BMT) and/or during a 24-hour Daily Living Observation (DLO).



9.3.3 Holter ECG setup tasks performed by the study staff

Before starting the ECG Holter recording, the following setup tasks have to be performed by the study staff.

- Open the ECG Holter device.
- Insert a new battery (Alkali-AAA, LR0) as provided (take a new one for every patient).
- Label CF card with patient ID
- Insert CF card.
- In case of a patient being an non-EPS candidate:
    - Attach the 10-patch interface (Varios yoke) as rear lid to the ECG Holter device.

- In case of a patient being a EPS candidate:
    - Attach the 3-patch interface (standard) as rear lid to the ECG Holter device.
- Safely close the ECG Holter device.
- Synchronize the ECG Holter clock to an appropriate clock, e.g. the clock of your mobile phone using correct local date and time, accurate to the minute (use Holter device menu 'Set up' → Time; navigate with yellow button and enter with green button).
- In case of a patient being an EPS candidate:
    - Prepare and attach three single ECG patch electrodes to the patient as depicted in Figure 9-1 and described in Table 9-2.
    - Connect the ECG Holter device (with the 3-patch interface) to the patch electrodes following the color codes as depicted in Figure 9-1 to ensure a correct step-by-step connection of one cable and one electrode.
- In case of a patient being a non-EPS candidate:
    - Prepare and attach ten single ECG patch electrodes to the patient as depicted in Figure 9-2 and described in Table 9-3.
    - Connect the ECG Holter device (with the 10-patch interface) to the patch electrodes following the color codes as depicted in Figure 9-2 to ensure a correct step-by-step connection of one cable to one electrode.
- Confirm ECG signal quality on the ECG Holter. At least two electrodes should have clear QRS complexes. Check the electrodes and cables where appropriate and reposition electrodes in case of ECG instability/poor quality.
- Use adequate tape (e.g. Ambu SkinFix) to attach the electrode cables and the thicker 10-patch interface (Varios yoke), respectively, to the patient's torso.
- Use strain reliefs (e.g. loop between electrode and adhesive tape) to compensate for patient movements such as stretching of the arms to avoid any accidental disconnection.
- Confirm ECG signal quality again. At least two electrodes should have clear QRS complexes. Check the electrodes and cables where appropriate and reposition electrodes in case of ECG instability/poor quality.
- Start the Holter ECG recording using on-screen menus (with green button).
- ECG signal can be displayed by simultaneous pressing of the green and yellow button.
- Secure the ECG Holter unit comfortably to the patient. At best, attach to a belt, or place in a pocket/pouch.

Additional documentation will be provided including more details on the setup tasks.

9.3.4 Body Motion Test (BMT)

For patients without EPS procedure, the BMT shall be performed. It comprises ECG recordings with various body positions, and activities to be performed after initialization of the Holter ECG recording. The Holter ECG with 10-patch electrode interface must be applied according to section 9.3.2.

Holter ECG setup tasks must be performed by the study staff according to section 9.3.3. After initialization of the Holter device, the recording shall run continuously throughout the whole BMT procedure unless there are compelling medical reasons for interruption.

The following activities must be supervised by the study staff during BMT.

- Instruct the patient that he or she will be performing a series of activities.

- Note the starting time of the supervised activities.
- Guide the patient through the following activities, press the green button on the Holter ECG and note the stopwatch time at which each activity is started. Each activity shall be performed for approx. 30 to 40 seconds and is followed by 20 to 30 seconds of rest before proceeding to the next activity:
    - Body position: Supine.
    - Body position: Right lateral.
    - Body position: Left lateral.
    - Body position: Prone (if applicable).
    - Body position: Seated.
    - Body position: Standing.
    - Body position: Standing with arms stretched out frontward.
    - Body position: Standing with arms extended out to sides.
    - Body position: Standing with arms stretched above the head.
    - Body position: Standing with alternating arm movements (one arm positioned next to the body and the other stretched above the head).
    - Tension movements: Seated with rubber band under feet, picking the ends of the rubber band with both hands, and alternating flexing/stretching the arms by leading hands to shoulders and back.
    - Tension movements: Seated/Standing with rubber band between hands, and alternating flexing/stretching the arms by leading hands out to sides and back.
    - Tension movements: Seated/Standing with rubber band between hands, arms above head, and alternating flexing/stretching the arms by leading hands out to sides and back.
    - Tension movements: Seated/Standing, pressing hands together in front of chest.
    - Activity: Slow walking.
    - Activity: Slow climbing stairs (up/downstairs) (if acceptable).
    - Activity: Faster walking.
    - Resting for 1 minute.

Additional documentation will be provided including more detailed instructions for the BMT.

9.3.5 24-hour Daily Living Observation (DLO)

A 24-hour Holter ECG is to be recorded from a non-EPS patient. The Holter ECG with 10-patch electrode interface must be applied according to section 9.3.2, and setup tasks must be performed by the study staff according to section 9.3.3. If the patient has just undergone ECG recording during BMT, the Holter device and setting as well as the already applied electrodes can be left as they are. In this case, the recording is already running and must not be restarted. Alternatively, the 24-hour Daily Living Observation can be done up to 14 days after enrollment.

Optionally, a 24-hour Holter ECG might be recorded from an EPS patient right after the EPS procedure or up to 14 days after enrollment. The Holter ECG with 3-patch electrode interface must be applied according to section 9.3.1, and setup tasks must be performed by the study staff according to section 9.3.3. If the patient has just undergone ECG recording during EPS, the Holter device and setting as well as the already applied electrodes can be left as they are. In this case, the recording is already running and must not be restarted.

Before the patient leaves to perform the unsupervised DLO, the patient shall be informed by the study staff on how to handle the 24-hour Holter device, especially

- that she/he should wear the Holter ECG device now for 24 hours while going about normal daily routine including all activities, but
- that she/he should avoid activities that might lead to the monitor getting wet, like taking a bath or shower;
- that magnetic and electrical fields may interfere with the function of the Holter monitor;
- that she/he or any relative may reattach a cable and/or patch electrode in case of a noticed dislodgement.

Furthermore, the patient must be informed by the study staff on how to keep the patient diary, especially

- Note the time of DLO start (time of leaving).
- Explain some examples to the patient.
- Remind the patient to bring back the diary at the scheduled visit.
- Note the time of DLO end (time of re-visit).

If the patient cannot return in person after completing the 24 hour DLO, he/she may be instructed on how to detach all electrodes himself/herself. An appointment shall be made to return the Holter ECG and the patient diary to the study staff.

9.3.6 Holter ECG completion and data retrieval

The following tasks have to be done after completion of a Holter ECG recording:

- Remove the Holter ECG device
    - Press the green button to set final marker.
    - Detach all electrodes from the patient and remove the ECG Holter device.
    - Open the ECG Holter device.
    - Remove both battery and CF card from the device.
    - Ensure labeling of CF card with correct patient ID.
    - Safely close the ECG Holter device.
- Ask for the patient diary form (in case a 24-hour ECG recording was performed)
- Provide data to the sponsor by sending CF Card and patient diary (pseudonymized with the patient ID) to sponsor.

9.4 Patient reimbursement

After completion of the Holter ECG recording, the patient will receive a compensation for his/her expenses and time. Reimbursements will be done by the sites according to the procedures as defined in the clinical trial agreement.

9.5 Termination

The patient's study participation ends regularly at the moment when the last study procedure according to protocol has been completed. The CRF 'Termination' has to be completed.

In case of any premature study termination, the CRF 'Termination' has to be completed with the reason for study termination. If the Holter ECG could not be completed successfully, the reason must be provided.

Follow-up of patients who have withdrawn consent is covered in section 8.3.4.2.

9.6 Description of those activities performed by sponsor representative

Sponsor representatives are not planned to take over specific activities. Yet, it might happen that sponsor representatives will support the investigator or his/her dedicated study team during the conduct of the Holter ECG recording, handling of the Holter ECG device or shipment/delivery of study equipment. Nevertheless, the investigator and the trained study team are responsible to adhere to the clinical investigation plan.

Monitoring will be performed by a sponsor representative according to the monitoring plan and as described in section 10.

9.7 Responsibilities

9.7.1 Responsibilities of the sponsor

The sponsor of the BIO|CONCEPT.ECG-Library study is:

BIOTRONIK SE & Co. KG
Woermannkehre 1
12359 Berlin
Germany

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

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

- Maintaining insurance cover or indemnification of subjects in case of injury in accordance with applicable laws.
- Contracting of investigational sites and investigators, specifically determining the agreement between sponsor and the research site with respect to such as but not limited to the following: conducting the contract research, obligations of the sponsor/the investigational site/the investigator, fee payments of the sponsor, intellectual property and publication of research results, confidentiality, insurance coverage and compliance with applicable laws/regulations and ethical standards. Selection of suitable investigational sites, investigators and clinical monitors.
- Obtaining of a favorable ethics vote(s) for conduct of the clinical study.
- Obtaining approval of the involved competent authorities (if applicable).
- Responsibility for all payments and financial coverage of the study.
- Supervision of study conduct according to the legal regulatory requirements and the requirements of the CIP.
- Fulfill reporting duties of the sponsor to the 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.

9.7.1.1 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 research associates, data assistants, data base managers).

9.7.1.2 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 CRF user guide.
- Data management.
- User Management

9.7.1.3 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.

9.7.1.4 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.

9.7.2 Responsibilities of the investigators

9.7.2.1 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.

9.8 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. As the investigator, the physician is responsible for conducting the study in accordance with the signed clinical trial agreement the clinical investigation plan, applicable laws, and/or local regulations and any conditions of approval imposed by the reviewing EC.

The entries in the CRF 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 (as applicable), and applicable laws and regulations to ensure adequate protection of the rights, safety and wellbeing of subjects and the quality and integrity of the resulting data.

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

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

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

1. Completion and submission of the required electronic case report forms (CRFs) and other applicable study documentation
2. Continued acceptability of the facilities
3. Adherence to the clinical investigation plan
4. Adherence to current version of ISO 14155 (as applicable) and local regulations and laws

If a monitor becomes aware that an investigator is not complying with the requirements mentioned above, the monitor is obliged to notify BIOTRONIK study management. BIOTRONIK will evaluate the non-compliance and issue corrective actions, discontinue enrollment or as a last measure close the clinical investigational site (see section 14 and 20)

11 STATISTICAL CONSIDERATIONS

11.1 Statistical design, method and analytical procedures

Exploratory data analysis will be used to describe the patient population.

11.2 Sample size

For this study, no statistical hypotheses can be formulated; therefore a sample size calculation is not applicable. However, at least six patients for each condition (see section 4.2) should be enrolled for the following reasons:

A minimum sample size of six would be needed to draw a conclusion with inferential statistics from binary data; e.g. to successfully apply a new algorithm in all 6 samples, a random effect can be excluded based on a 5 % significance level with an exact 95 % confidence interval larger than 50 %. Since ventricular tachycardia is most important in the development of certain detection algorithms, a minimum of ten patients is foreseen. Thus, in case of a successful application of a new algorithm in 10 of 12 samples, a random effect can be excluded based on a 5 % significance level. Consequently, 13 x 6 + 12 = 90 patients should be at least enrolled. Due to an assumed rate of 10 % non-evaluable ECG recordings, at least 100 patients should be enrolled in the study. However, due to the conditions defined for replacements of patients (section 8.1.4) and a potential time delay in ECG analysis by the sponsor (section 8.1.3.3), the total number of enrolled patients might exceed the planned sample size.

11.3 Expected drop-out rate

It is expected that at least 10 % of the enrolled patients can only be partly included or not at all in the analysis of data, e.g. due to withdrawal of consent, refusal to participate in the Holter ECG or premature termination without documentation of the intended ECG pattern.

11.4 Pass/fail criteria

Not applicable.

11.5 Provision for an interim analysis

As there is no hypothesis to test, no comprehensive interim analysis is planned at a certain point in time. The acquired data will be continuously forwarded to the technical department for analysis.

11.6 Termination criteria

Not applicable

11.7 Procedures for reporting of deviations to the statistical plan

If deviations to the statistical plan become necessary for the clinical report, the changes and the reason(s) for the changes will be reported in the clinical report.

11.8 Specification of subgroups

There are no pre-defined sub-groups.

11.9 Procedure for accounting of all data for analysis

Due to the use of the electronic data capture and the required strict adherence to the monitoring plan, an adequate data acquisition of all data is ensured.

11.10 Handling of missing, unused and spurious data

Missing or spurious data will not be imputed.

11.11 Exclusion of data from confirmatory data analysis

In the following cases, data is 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

Details are provided in the Statistical Analysis Plan.

11.12 Minimum and maximum number of patients per site

There is no maximum or minimum number of patients per site.

12 DATA MANAGEMENT

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.ECG-Library 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 (CRF). 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 (Regulation (EU) 2016/679 (incl. Corrigendum dated 23 May 2018), 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 Principal Investigator (PI) as well as those co-investigators to whom the PI delegates data entry and authorization of CRFs needs 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 CRF entries, source data needs to be maintained at the site and will be collected in adequate files (e.g. patient files). The data have to be stored and shall be made available upon request in order to allow source data verification. Exceptions for which the CRF entry can be regarded as source data are indicated in the Monitoring plan or in 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 CRF 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 CRF 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 CRF 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 the 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 CRF 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.

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

Not applicable.

16 STATEMENT OF COMPLIANCE

16.1 Applicable ethical standards

The study will be conducted in compliance with the principles that have their origin in the Declaration of Helsinki (current version). 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'. With regard to the exploratory character of this study and since no investigational device will be used in the study, the following deviations to ISO 14155:2011 occur:

- No investigational device will be used in the study, therefore no dedicated Investigator's Brochure or Instructions for Use are provided.
- No coordinating investigator has been nominated for this multicenter study, as only documentation of Holter ECGs occur during the patient's study participation which does not require additional coordination between the PIs, nor medical advice.
- No investigational device will be used, therefore no device deficiencies and (S)ADEs will be reported
- No investigational device will be used, therefore no investigational device accountability is necessary

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

16.3 Ethics committee and competent authority

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

16.4 Statement of adherence to additional requirements

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

16.5 Statement on subject insurance

All participants of this clinical study are insured against study related injury according to applicable provisions of law.

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

17 INFORMED CONSENT PROCESS

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

17.1 General considerations

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

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

Date 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 the patient is unable to write, consent may be given and recorded through appropriate alternative means in the presence of at least one impartial witness, who then signs and dates the informed consent form.

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

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

17.2 Special circumstances for informed consent

Not applicable.

18 ADVERSE EVENTS

In the course of the clinical investigation, undesired medical events can occur in participating patients, which are called adverse events (AEs) in the following. All AEs 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 CRF 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 procedures involved.

Since no investigational devices are used in this study, the references to 'investigational devices' are not applicable.

*see ISO 14155:2011 3.2

18.2 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 14155:2011 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.

18.2.1 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 pseudonymized copy of the death records, an autopsy report (if performed) and a doctor´s letter detailing the medical history and the circumstances of the death should be sent to BIOTRONIK promptly.

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

- Cause of death
- Date and time of death

- Place death occurred
- Device status at the time of death
- Statement whether the event was device or study procedure related

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

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

18.3 Anticipated adverse events

Risks of Holter Monitoring are rare, but may include skin irritation at the application site of the adhesive electrode patches. In addition, the patient may experience a discomfort caused by wearing the ECG patches, the Holter ECG device, or the cabling of the device. Discomfort or dizziness may also occur during the study specific activity tests and/or position of the subject during the recordings.

In addition, the procedure may reveal previously undetected medical conditions or device issues. These conditions will be treated according to the physician's discretion.

18.4 Reporting responsibilities

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

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)AEs 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.

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 pseudonymized 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.

18.4.2 Reporting responsibilities of the investigator to other parties

According to national and international regulations some of the involved competent authorities (CAs) and ethics committees define specific safety reporting requirements. Investigators have to ensure, that they fulfil these local reporting obligations given by their competent authorities and ECs, in case they are more restrictive than the general requirements stated in the section reporting timelines below.

18.4.3 Reporting responsibilities of the sponsor

BIOTRONIK SE & Co. KG will report all serious Adverse Events (SAEs) 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 on a regular basis.

18.5 Reporting timelines

The reporting timelines for the investigator are displayed in Table 18-1.

Table 18-1: Reporting timelines.

Event	Report to	Timeline
Adverse Event (AE)	CCR BIOTRONIK SE & Co. KG: Documentation in the AE CRF	Preferably within 2 weeks
Serious Adverse Event (SAE)	CCR BIOTRONIK SE & Co. KG: Documentation in AE-CRF	Immediately, latest 24-hour after detection

The obligation to assess and report SAEs 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.

18.6 Emergency contact

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

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 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.
- No enrollment in one of the subgroups mentioned in section 8.3.2 for at least 30 days
- 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 CRF for 'Termination' has to be completed in all of the above cases.

All open CRFs 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 required 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)AE 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'.

Patients have to be informed on this procedure in written form in the patient informed consent form.

21 PUBLICATION POLICY

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

Due to the nature of the study, no publication of the results is planned.

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