Clinical Investigation Plan

for the

BIO|Sync-HUTT

Head-up Tilt Test in patients with reflex syncope and asystolic response who received a dual-chamber pacemaker with the Closed Loop Stimulation (CLS) and participated in the BIOSync trial

Reference number:	BA117
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Investigational device:	Dual-chamber pacemaker with CLS feature

Revision History:

Title	Scope	Key words	Date
CIP 2-0 Amendment 1	ALL sites	Change of the exclusion criterion No. 2 (substantial)	20-Apr-2022

Coordinating Investigator

[redacted]

IRCCS Istituto Auxologico Italiano

Faint & Fall programme, Dept. of Cardiovascular, Neural and Metabolic Sciences, Ospedale San Luca

Piazzale Brescia, 20

20149/Milano (MI), Italy

Director Clinical Project Management

[redacted]

BIOTRONIK SE & Co. KG

Center for Clinical Research

Woermannkehre 1

12359 Berlin, Germany

Clinical Project Manager

[redacted]

BIOTRONIK SE & Co. KG

Center for Clinical Research

Woermannkehre 1

12359 Berlin, Germany

Sponsor

BIOTRONIK SE & Co. KG

Woermannkehre 1

12359 Berlin, Germany

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 eTMF.

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
ASADE	Anticipated Adverse Device Effect
BP	Blood Pressure
CA	Competent Authority
CDMS	Clinical Data Management System
CE	CE mark, a stylized "CE" (Conformité Européenne) placed on products to signify conformance with European Union regulations
CI	Coordinating Investigator
CIP	Clinical Investigation Plan
CIR	Clinical Investigation Report
CLS	Closed Loop Stimulation
CRF	Case Report Form
DD	Device Deficiency
eTMF	electronic Trial Master File
EC	Ethics Committee
FU	Follow-up visit
HR	Heart rate
HUTT	Head-Up Tilt Test
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (www.ich.org)
IEGM	Intracardiac Electrocardiogram
IRB	Institutional Review Board
IFU	Instructions For Use (user manual)
iMedNet	Web-based electronic data entry (EDC) system for clinical trials provided by MedNet Solutions Inc.
ISO14155	International Organization for Standardization, norm no. 14155
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistics and Analysis Software produced by SAS Institute Inc. www.sas.com)
SDS	Source Data Sheet
SV	Stroke Volume
TPR	Total Peripheral Resistance

2 SYNOPSIS

Title	BIO|Sync-HUTT
Patient population	The study will select patients with reflex syncope and positive cardioinhibitory response to Head-Up Tilt Test (HUTT) who had already participated in the BIOSync study.
Design	Prospective, non-randomized, multi-center, observational, acute study.
Investigational device(s)	The closed-loop stimulation (CLS) algorithm implemented in current dual-chamber pacemakers manufactured by BIOTRONIK.
Objectives	To provide standardized, complete and quality controlled data sets with parameters that describe hemodynamic changes and their timing with respect to CLS pacing activation during reflex syncope induced by HUTT.
Data of interest	a) Heart rate, blood pressure, stroke volume, and peripheral resistance at the following time-points during HUTT: • Time of maximum spontaneous heart rate (end of phase 1/beginning phase 2 of the reflex); • Time of pacing onset; • Time of recovery of spontaneous rhythm after pacing (end of recovery period); • time of syncope (i.e. loss of consciousness) during HUTT (also assessed by video recording if available at investigational site); • time of tilt-down (supine patient position just after tilt-down); b) Above-mentioned times of interest expressed as intervals (MM:SS) from the start of the HUTT c) Duration of the recovery phase (interval from maximum pacing rate to basic rate or spontaneous rhythm expressed in MM:SS from the start of the HUTT) d) Slopes in heart rate (bpm per sec) and systolic blood pressure (mmHg per sec) during the recovery phase

Title	BIO|Sync-HUTT
Inclusion criteria	• Ability to understand the nature of the study. • Willingness to provide written informed consent. • Patients undergoing HUTT for monitoring of syncope, therapy adjustment, training or other medical reasons during ordinary follow-up, irrespective of study participation. • Patients who participated in the BIOSync study*. • Patients with a dual-chamber pacing system equipped with the CLS algorithm. * If needed, inclusion of other patients who did not participate in the BIOSync study will be considered to complete study cohort, provided that they have already a CLS pacemaker system and fulfill the same inclusion/exclusion criteria of the BIOSync study.
Exclusion criteria	• Pregnant or breast feeding women. • Age less than 40 years. • Patients who after the BIOSync study participation have developed the following: - Any indication to pacemaker different from reflex syncope with positive HUTT response; or - Any classified indication to implantable defibrillator, cardiac resynchronization therapy according to current guidelines; or - Any cardiac dysfunctions likely leading to loss of consciousness
Study duration	~ Q1 2022 – Q3 2023 (~ 19 months)
Sample size	A total of 20 patients will be included in the study.
Number of investigational sites	The study will be conducted in at least 2 sites.
Number of follow-ups per patient	This is an acute study. Investigational procedures will be conducted at any HUTT performed according to routine clinical practice. Patients who undergo HUTT during ordinary follow-up visits irrespective of study participation, are eligible. The study has no additional follow-ups after HUTT execution.
Coordinating investigator	[redacted]
Boards (if applicable)	None

Title	BIO|Sync-HUTT
Sponsor	BIOTRONIK SE & Co. KG Center for Clinical Research Woermannkehre 1 D-12359 Berlin

In this investigational study the term 'patient' is identical with the term 'subject' as defined in ISO 14155, because all study participants are patients treated by physicians at the investigational sites.

3 INTRODUCTION

The 2021 European Society of Cardiology guidelines recommend cardiac pacing in patients aged >40 years with tilt-induced asystolic reflex syncope (class I, level of evidence A). (1) The recommendation relies on recent results from the multicentre, randomised, double-blinded, parallel-design BIOSync trial. (2) The BIOSync study provided evidence of benefit of dual-chamber pacing in patients with tilt-induced reflex syncope and confirmed the role of Head-up Tilt Table (HUTT) test as a diagnostic method for cardiac pacing in reflex syncope. The study randomised patients aged ≥40 years with frequent reflex syncope and VASIS 2B cardio-inhibitory response to HUTT to receive either an active or an inactive dual-chamber pacemaker with the CLS pacing mode. The rationale for pacing with CLS in cardioinhibitory reflex syncope was recently reviewed by Tomaino et al. (3) CLS is able to measure changes in intracardiac impedance during the systolic phase of each cardiac cycle which are strictly correlated to the increased heart rate and right ventricular contraction speed which are usually present during the pre-syncope phase of the reflex. It was hypothesized that an early onset of CLS pacing may be triggered by the compensatory increase in heart rate to counteract vasodilation and pressure drop during the pre-syncope phase of the reflex. The BIOSync study showed a 77% reduced risk of syncope in the DDD-CLS group as compared to pacing off. The design of the BIOSync study did not allow to assess the specific effect that CLS adds to dual-chamber pacing. Despite DDD-CLS pacing, 22% of patients had syncopal recurrence in 2 years. Further investigations are therefore needed in order to reduce this failure rate. Indeed, it is still unclear whether syncopal recurrences should be ascribed to dominant vasodilation or if the CLS programming/functioning needs optimization to more adequately sustain cardiac output during reflex in these specific cases. (3) The purpose of this study is to explore changes in hemodynamic parameters during HUTT and their timing with respect to CLS pacing activation. This study may add knowledge to better understand the mechanisms underlying recurrent syncopal events and optimal pacing programming.

4 DEVICE(S) USED IN THE STUDY

The following devices, tools and accessories will be used during the study:

- the CLS algorithm (as investigational device in this investigation according to, ISO14155) implemented in current dual-chamber pacemakers manufactured by:

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

- RENAMIC programmers or later models;
- Any external monitor capable of measuring continuously patient's hemodynamics (e.g. Task Force Monitor);
- Standard equipment needed for the HUTT execution.

Such devices must be available at the investigational sites before study participation and will not be provided by the Sponsor.

4.1 Model name including software version and accessories

All models of current dual-chamber pacemakers manufactured by BIOTRONIK implementing the CLS algorithm may be included in the study. Devices are used along with any CE-marked leads. A detailed description of the pacing systems is reported in their user manual.

4.2 Description of traceability

All medical devices used in the study will be tracked by serial numbers.

4.3 Intended purpose of the device(s) in the study

All above-mentioned medical devices are CE-certified and will be used within their intended use and according to their user manual.

4.4 Intended patient population and indications

Pacemakers included in this study are used for all bradycardia arrhythmia indications to improve patients' symptoms that can be clinically manifested and compensate bradycardia by atrial, ventricular or Atrio-Ventricular sequential pacing.

The intended study population consists of patients who have indication for the pacemaker therapy according to the current European guidelines. (1) BIOTRONIK pacemakers equipped with CLS are therefore used within their indication.

4.5 Description of the CLS algorithm

The CLS algorithm was developed to provide a physiologic pacing rate modulation in response to metabolic demand and it is based on an analysis of the right ventricle unipolar impedance trend during systole. Impedance trend is obtained by sampling with high frequency subthreshold pulse train: an increase of the impedance trend slope, with respect to a (rest) reference, is an indication of an increased metabolic demand and it is used to adapt heart rate accordingly. In particular, impedance changes depend on the amount of blood and myocardial tissue in the volume surrounding the tip of the right ventricular lead. During contraction, blood ejection causes tighter electrode contact with myocardial tissue (involving a larger proportion of tissue relative to blood volume), leading to a progressive impedance increase towards late systole (3). CLS automatically increases pacing rate in response to detected changes in myocardial contractility. CLS functioning actively interacts with the autonomic regulation

process of cardiac output, occurring under several conditions of everyday life, not limited to exercise. (4)

4.6 Summary of training and experience needed

All investigators must dispose of adequate research training and experience. Training on ISO 14155 and/or several years of experience in conducting clinical trials are generally required.

In addition to having basic medical knowledge, investigators must be thoroughly familiar with cardiac pacing and conduction of HUTT Investigators will be trained on the study procedures.

5 JUSTIFICATION FOR THE DESIGN OF THE CLINICAL INVESTIGATION

Although cardiac pacing is recommended in population investigated in this study, there is still a number of them who experience syncopal recurrences despite pacing. A better understanding of physiology of syncopal reflex and the effect of cardiac pacing is needed. To this purpose, an exploratory study design without additional follow-ups after HUTT executed as per standard clinical practice was chosen. There are no endpoints in this study due to its exploratory design without statistical hypotheses to be tested. The in- and exclusion criteria are defined in a way to select patients from the BIOSync study for whom the performance of dual-chamber pacing with CLS was already documented allowing to better correlate new insights from this study with the benefit of therapy. A rationale for the chosen sample size is given in section 12.5.

All devices are CE-certified and used according to their indication and user manual. Therefore, the use in human subjects is justified.

6 BENEFITS AND RISKS OF THE DEVICE, CLINICAL PROCEDURE, AND CLINICAL INVESTIGATION

6.1 Anticipated clinical benefits

Participating subjects will benefit from an accurate programming of cardiac pacing and CLS function, based on the detailed evaluation of pacing activation during the reflex induced by the HUTT. This may help further prevent syncopal relapses.

6.2 Anticipated adverse device effects

No additional risks related to the CLS function or the equipment used for HUTT are expected resulting from the participation in the study. Study patients have already received pacemaker therapy according to current guidelines. Anticipated Adverse Device Effects (ASADE) associated with pacemaker therapy are described in section 19.8.

Participating patients will undergo HUTT as per standard clinical practice. No serious adverse events related to the HUTT are expected in literature except for known adverse effects of nitroglycerine. These may include: dizziness, weakness, palpitations, vertigo, headaches, nausea, vomiting, diaphoresis, syncope, hypotension, pallor, flushing, exfoliative dermatitis, drug rash (5-7).

6.3 Risk associated with participation in the clinical investigation

The investigational procedures performed during routine patient follow-up do not involve additional risks for the enrolled subjects. Participating patients will undergo a HUTT examination at enrollment visit according to their normal follow-up schedule. HUTT is a safe procedure and often considered as part of normal clinical practice in the study population, even after pacemaker implant, to predict response to or adjust therapy. There have been reported neither deaths nor severe complications during the tests.

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

6.4 Possible interactions with concomitant medical treatments

No interactions are expected with medical treatments.

6.5 Steps to control or migrate the risk

Careful selection of participants and accurate conduction of HUTT according to the procedures described in section 9 will allow to minimize potential risks.The following measures shall be taken during a HUTT:

- Adherence to relevant medical guidelines
- Use of nitroglycerine during active phase of the HUTT
- Resuscitation equipment available and trained personnel during test procedures

Study staff will be trained at study start (Initiation Visit) and periodically re-trained if necessary.

6.6 Rationale for benefit-risk ratio

As no additional risks are expected in association with study procedures, as described in sections 6.2 to 6.5, expected benefits reported in section 6.1 outweigh risks. In addition, the knowledge gained from the study will help improve diagnosis and treatment of patients with reflex syncope and asystolic HUTT response.

7 OBJECTIVES AND HYPOTHESES

7.1 Purpose of the clinical investigation

The purpose of this study is to add knowledge to better understand the hemodynamic mechanisms underlying recurrent syncopal events and optimal pacing programming.

7.2 Objectives (Endpoints)

This study will provide standardized, complete and quality controlled data sets with parameters that describe hemodynamic changes and their timing with respect to CLS pacing activation during reflex syncope induced by HUTT.

7.3 Hypotheses

Due to the exploratory design of the study there are no statistical hypotheses (null/alternative hypotheses) associated with study objectives.

7.4 Risks and anticipated adverse device effects

There will be assessments of risks and anticipated adverse device effects throughout the clinical investigation as described in section 19.

Anticipated adverse device effects and risks associated with participation in the clinical investigation are described in subchapter 6.2 and 6.3.

8 DESIGN OF THE CLINICAL INVESTIGATION

8.1 General considerations

8.1.1 Design type of clinical investigation

The study is designed as a prospective, non-randomized, multi-center, observational acute study without additional follow-ups after HUTT execution.

8.1.2 Measures taken to minimize or avoid bias

Accurate patient selection as described in section 8.2 and precise conduction of HUTT according to the procedures described in section 9 will allow to minimize potential confounding factors.

8.1.3 Data of interest

a) Heart rate, blood pressure, stroke volume, and peripheral resistance will be collected at the following time-points during HUTT:
   - time of maximum spontaneous heart rate (end of phase 1/beginning phase 2 of the reflex);
   - time of pacing onset;
   - time of recovery of spontaneous rhythm after pacing (end of recovery period);
   - time of syncope (i.e. loss of consciousness) during HUTT (also assessed by video recording if available at investigational site)
   - time of tilt-down (supine patient position just after tilt-down)

b) Above-mentioned times of interest (expressed in HH:MM:SS from the start of the HUTT)

c) Duration of the recovery phase (interval from maximum pacing rate to basic rate or spontaneous rhythm expressed in MM:SS from the start of the HUTT)

d) Slopes in heart rate (bpm per sec) and systolic blood pressure (mmHg per sec) during the recovery phase

Definitions.

Phase 1 of reflex during HUTT is defined as the interval from the start of blood pressure decrease due to a reduced venous return (and consequent corrective heart rate increase) to the beginning of phase 2.

Phase 2 is characterized by decrease of heart rate due to the activation of vagal reflex. Phase 2 (HR drop) may be partially masked by pacing activation.

Recovery phase is defined as the interval from maximum pacing rate to basic rate or spontaneous rhythm, if pacing is not delivered.

8.1.4 Methods

8.1.4.1 CRFs

All parameters and measurements that are recorded within the registry are documented on the corresponding electronic case report forms (CRFs) listed below. The investigator is required to use an electronic signature to approve the content of the data reported in the CRFs.

Following CRFs are used:

- Enrollment/Baseline Form
- Device Interrogation Form
- HUTT Form
- Adverse Event/Device Deficiency Form
- Study Termination Form

The corresponding time schedule is described in Section 9.

8.1.4.2 Source Data Sheets

For HUTT data collection the following Source data sheets (SDS) are recommended to be used:

- HUTT examination (preparation phase) SDS
- HUTT examination (execution phase) SDS

8.1.5 Equipment to be used for the assessment of variables

Implanted device and related equipment are described in Section 4.

Patients will undergo HUTT exam as per clinical practice during ordinary follow-ups irrespective of study participation. This test will require the use of standard CE-marked equipment, such as tilt tables and tools to electronically record continuous data on HR, BP, SV, and TPR. Time of syncope may be assessed also by video-recording (if available at the investigational site).

8.1.6 Replacement of patients

A total of 20 subjects who had been already enrolled in the BIOSync study will be asked to participate in the present BIO|Sync-HUTT study. If less than 20 BIOSync patients will accept to participate for any reasons, participants may be replaced until fully analysable data set will be collected from 15 participants.

Replacements will consist of patients who already received a dual-chamber pacemaker with the CLS function who meet the same subset of inclusion/exclusion criteria of the BIOSync study (8).

8.1.7 Investigation sites

The study will be conducted in at least 2 investigational sites that already participated in the BIOSync trial.

8.1.8 Completion of the clinical investigation

The study will be completed when the last visit of the last subject will be available and documented in the CRFs (as defined in section 8.1.4.1).

8.2 Patients

The intended patient population consists of all patients with reflex syncope and positive cardioinhibitory response to HUTT who had already participated in the BIOSync study. As described in section 8.1.6 replacements are allowed, if needed.

8.2.1 Inclusion criteria

- Ability to understand the nature of the study.
- Willingness to provide written informed consent.
- Patients undergoing HUTT for monitoring of syncope, therapy adjustment, training or other medical reasons during ordinary follow-up, irrespective of study participation
- Patients who participated in the BIOSync study*.
- Patients with a dual-chamber pacing system equipped with the CLS algorithm.

* If needed, inclusion of other patients who did not participate in the BIOSync study will be considered to complete study cohort, provided that they have already a CLS pacemaker system and fulfill the same inclusion/exclusion criteria of the BIOSync study.

8.2.2 Exclusion criteria

- Pregnant or breast feeding women.
- Age less than 40 years.
- Patients who after the BIOSync study participation have developed the following:
  - Any indication to pacemaker different from reflex syncope with positive HUTT response; or
  - Any classified indication to implantable defibrillator, cardiac resynchronization therapy according to current guidelines; or
  - Any cardiac dysfunctions likely leading to loss of consciousness (overt heart failure, ejection fraction <40%, myocardial infarction, diagnosis of hypertrophic or dilated cardiomyopathy, clinically significant valvular disease, sinus bradycardia <50 bpm or sinoatrial block, Mobitz I second degree atrioventricular block, Mobitz II second or third-degree atrioventricular block, complete bundle-branch block).

8.2.3 Criteria and procedures for subject withdrawal

8.2.3.1 Withdrawal of patient consent

Patients may withdraw their consent for study participation at any time without stating the reason and without any unfavourable consequences. All data that is collected until the date of withdrawal will be deleted immediately by effective anonymization, unless their further processing is still required as regulated by the legal exceptions to the deletion obligations. This also applies if the patient has requested data erasure. Depending on the patient's decision to delete the data, it will be deleted by effective anonymization as soon as the conditions for the

legal exceptions on further retention and processing cease to apply. A withdrawal sheet and a study termination CRF have to be filled in by the investigational site.

8.2.3.2 Impossibility of device programming at enrolment visit

If during the enrolment visit a device programming according to Table 2 (as reported in section 9.2.2) is not possible for any reason, the patient shall terminate study participation before performing the HUTT (dropout).

8.2.4 Point of enrollment

A subject is considered enrolled in the BIO|Sync-HUTT Study upon the signature of the Informed Consent Form after confirmation of the elegibility criteria by the investigator.

8.2.5 Total expected duration of the clinical investigation

The expected total duration of the study is 19 months after the first enrolment.

8.2.6 Expected duration of each subject's participation

Subjects participate from consent to HUTT execution with not further follow-up. Figure 1 shows the flowchart of the study.

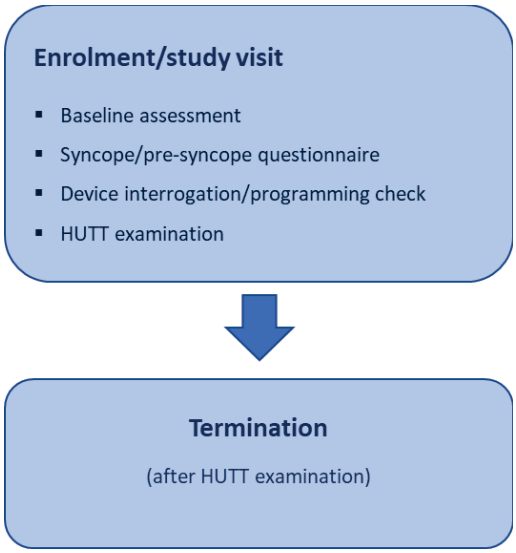


Figure 1: Flowchart for the BIO|Sync-HUTT study

8.2.7 Number of subjects required to be included

A maximum of 20 subjects will be enrolled (including replacements as described in section 8.1.6). Please refer to section 12.5 for further details on the planning of the sample size.

8.2.8 Estimated time needed to select patients

The enrolment period is expected to last 9 months.

9 STUDY PROCEDURES

9.1 Overview

This section describes all the study-related procedures as listed in Table 1 which will be performed during a routine scheduled patient follow-up.

Prior to obtaining informed consent, the patient's background and medical history will be reviewed in order to ensure he/she is an appropriate candidate for the study. Patient who undergo HUTT during ordinary follow-up visits irrespective of study participation, is eligible. After the patient has been determined to be eligible for the study, written informed consent will be obtained and demographic and medication data will be collected. Syncope and pre-syncope questionnaires will be self-administered. Prior to the HUTT, pacemaker interrogation will be performed in order to check programming settings and to collect device diagnostics. The HUTT may be performed and also recorded by a high-definition camera if available. Full hemodynamic parameters and ECG traces will be acquired during the HUTT. Any collected data and adverse events will be documented in an electronic CRF.

Table 1: Investigation Schedule

Investigations	Enrollment/study visit
Verification of in- and exclusion criteria	X
Patient informed consent	X
Demographic data	X
Medical history	X
Co-morbidities	X
Medication therapy	X
Patient self-administered syncope and pre-syncope questionnaires	X
ECG	X
Device programming settings and diagnostics	X
Head-up tilt test (including video recording if available)	X
Collection of primary and secondary endpoint-related measurements	X
(S)AE, (S)ADE, DD monitoring	X

9.2 Enrollment/study visit

9.2.1 Baseline assessment

The baseline data will be collected after consenting procedures are completed.

For baseline evaluation, the investigator collects the following data on an CRF:

- Demographic data
- Medical history
- Comorbidities
- Cardiomyopathies
- Arrhythmias
- Prior ECG
- Medication therapy
- Syncope and pre-syncope questionnaires
- Previous participation in the BIOSync study
- Date of pacemaker implantation
- Device programming

9.2.2 Study procedures after baseline assessment

The following procedures shall be conducted after baseline assessment:

- Interrogate the pacemaker and save the pacemaker diagnostics;
- Make sure that the DDD-CLS pacing mode has been activated since for at least 10 days. If the CLS mode is not active or any pacing mode other than DDD-CLS is active at the time of interrogation, reprogram the device as reported in the Table 2 below, and reschedule a new visit in at least 10 days to perform the HUTT. If device programming according to Table 2 is not possible for any reason, the patient shall terminate study participation before performing the HUTT (dropout).
- Perform standard tests to assess correct pacing and sensing function with current settings;
- Check that the device programming is set as reported in Table 2. Parameters which

are not listed have to be intended freely selectable*;

- Switch off the programmer;
- Perform the head-up tilt testing as reported in section 9.2.3;

*** Note: any device re-programming involving a switch from CLS-OFF to CLS-ON or a change in the CLS-mode pacing will require to postpone HUTT execution for at least 10 days. Any other device re-programming according to table 2 will require patient to wait 10 minutes in a sitting position before HUTT execution due to the time period needed to fine-tune impedance reference waveforms. Also it shall be ensured that the nominal AV-delay (excluding hysteresis) is programmed sufficiently short (intrinsic conduction time minus at least 43 ms) in order to avoid fusion beats.**

As per standard of care, PM programming will be optimized if needed, according to observations collected during the HUTT.

Table 2 – Device programming

Parameter	
Pacing Mode	DDD-CLS
Basic rate	50 bpm
Maximum CLS rate	120 bpm
Upper tracking rate	130 bpm
Atrioventricular delay	Low; 180–140 ms
Atrioventricular hysteresis mode	IRSplus
CLS Resting Rate Control	OFF
Atrial pacing polarity	Unipolar
Ventricular pacing polarity	Unipolar

9.2.3 Head-up tilt test

The HUTT will be performed according to the Italian protocol (9) and patient's hemodynamics will be continuously monitored during the entire test. Specifically, an external monitor will be used for continuous measurement and recording of systolic and diastolic BP, HR, SV, and TPR.

Prior to the start of the HUTT, a trained member of the study team will prepare the patient and set up the equipment needed for the test as follows:

- patient shall be supine on the tilt table and secured to it with the BP sensor cuff of the external monitor on his/her finger. Hand wearing the pressure sensor shall be placed on the chest at about 10 cm from heart and held in this position throughout the test;
- ECG leads shall be placed on patient’s chest and a BP cuff on his/her arm;
- If used, a high-definition camera may be placed to contemporarily pick up both patient and the external monitor positioned close to the tilt table.

  Note: video recordings of the entire test shall not be provided to the Sponsor and will be destroyed immediately after the examination. The investigator will assess the time of symptoms onset and will report it in the CRF.

After 10 minutes in supine position, the patients will be tilted to 70° using an electronically operating tilt-table with a footboard.

9.2.3.1 Timing of tilt down

In this study the HUTT will not be performed for diagnostic purposes but rather to verify the proper functioning of the implanted pacemaker. Therefore, HUTT is aimed to induce the vasovagal reflex, confirmed by the onset of symptoms and by onset of pacing and not to induce syncope. Given ethical issues, the table will be tilted down at the time of loss of consciousness. In case of negative test, the table will be tilted down at the end of test-time.

The following procedures shall be conducted after HUTT completion:

- Document outcome measurements on the CRF;
- Provide continuous electrocardiogram traces printed at 5 mm/sec from the time of maximum spontaneous HR increase during phase 1 until the end of the exam.

9.3 Termination and post treatment

The patients terminate the study regularly after the completion of the enrollment visit including HUTT and collection of study data. The CRF 'Study termination' has to be filled in. In case of any premature study termination, the CRF Study Termination has to be completed with the reason for study termination. The process of consent withdrawal is described in section 8.2.3.1.

After study termination the patients will continue to be treated according to standard routine care. The device programming is at the investigator's discretion.

9.4 Description of those activities performed by sponsor representative

Sponsor representatives may support the investigator for pacemaker programming and interrogation or for the download of data of the programmer as needed.

Monitoring will be performed by Sponsor representatives according to the monitoring plan.

9.5 Possible influencing factors on outcome or interpretation of results

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

10 RESPONSIBILITIES

10.1 Responsibilities of the sponsor

The sponsor of the BIO|Sync-HUTT 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 patients in case of injury in accordance with applicable laws.
- Contracting of investigational sites and investigators.
- Responsibility for all payments and financial coverage of the study.
- Selection of suitable investigational sites, investigators and clinical monitors.
- Creating a Master template for informed consent form and obtain approval of the Master template by the leading ethical committee (EC), if required.
- Obtaining of a favorable ethics vote(s) for conduct of the clinical study.
- Obtaining approval of the involved competent authorities (if applicable).
- 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.

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 research associates, data assistants, data base managers).

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 CRF user guide.
- Data management.

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.

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 11 of this document.

10.2 Responsibilities of the investigators

10.2.1 Coordinating investigator

This study is coordinated by:

[redacted]

IRCCS Istituto Auxologico Italiano

Faint & Fall programme, Dept. of Cardiovascular, Neural and Metabolic Sciences, Ospedale San Luca

Piazzale Brescia, 20

20149/Milano (MI), Italy

The responsibilities of the CI are listed in the following:

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

The coordinating investigator is supported by the clinical Project Manager and other members of the sponsor.

In addition, the CI has the same rights and duties as other principal investigators.

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.
- Safeguarding the rights of the physical and mental integrity as well as the privacy and the protection of the data of the study patients.
- 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, in case a patient has already been enrolled into another interventional clinical investigation without undue delay. Obtain the sponsors permission before enrolling the patient into another interventional clinical investigation.
- Conduct of the study according to the CIP
- Provide the sponsor with a ISO14155 training documentation
- Data collection and data entry in accordance with the requirements of the CIP. Patient records shall include the relevant medical history and progress of the disease of each patient.
- 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.

11 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 investigational device is used under the immediate direction of an investigator. As the investigator, the physician is responsible for conducting the study in accordance with the signed clinical trial agreement, the clinical investigation plan, applicable laws, and/or local regulations and any conditions of approval imposed by the reviewing IRB/EC.

The entries in the CRF will be reviewed and source data verified at the investigational site by monitors (authorized BIOTRONIK personnel, 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 laws and regulations to ensure adequate protection of the rights, safety and wellbeing of patients and the quality and integrity of the resulting data.

A monitor will visit the study site periodically during the study. All participating sites will be monitored during the course of the study with visits occurring as frequently as deemed necessary to ascertain adherence to the protocol procedures, as well as maintenance of the highest quality data. A detailed monitoring plan developed by BIOTRONIK will be followed.

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

Periodic monitoring visits and 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 and local regulations and laws
5. Availability and correctness of the signed patient informed consent

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.

A monitoring plan will be prepared as additional document. It provides detailed information about frequency and extent of monitoring.

12 STATISTICAL DESIGN AND ANALYSIS

12.1 Analysis population

All patients with valid patient informed consent are included in the analysis set.

12.2 Descriptive statistics

Standard descriptive statistical methods are used depending on the type of the available data. For continuous variables, mean value, standard deviation, median, minimum, maximum and quartiles are calculated. For nominal variables, absolute and relative frequencies are calculated based on non-missing data. For ordinal variables, median, minimum, maximum and quartiles or absolute and relative frequencies are calculated for each category based on non-missing data.

12.3 Analytical procedures

Standard inferential statistical methods are used depending on the type of the available data. For mean values, confidence intervals are calculated based on a t-distribution. For relative frequencies, confidence intervals are calculated based on a binomial distribution. Thereby, the significance value specified in the following sub-chapter is considered.

12.4 Significance level, statistical power, and statistical testing

Because there are no pre-specified hypotheses, all analyses are exploratory. However, a result of a two-sided statistical test with a p-value less than 5% or a one-sided statistical test with a p-value less than 2.5% is considered statistically significant.

For any inferential analyses, the result of a two-sided statistical test with a p-value less than 5% or a one-sided statistical test with a p-value less than 2.5% is considered statistically significant.

12.5 Sample size

Since the study has an exploratory design without hypotheses to be tested, the sample size cannot be based on a specific calculation. The sample size was chosen considering the objective of the study to understand hemodynamic mechanisms underlying syncope recurrences and CLS activation during HUTT. Based on such objective, a sample size of 20 was chosen without need for a lager number of patients. (10-13)

12.6 Interim analyses

There are no pre-planned interim analyses.

12.7 Bias

In case of a clear evidence of bias, which was not considered before, the Statistical Analysis Plan (SAP) is updated to avoid any bias.

See also chapter 8.1.2.

12.8 Subgroups

There are no pre-specified subgroups. However, some comparisons may be worth performing, e.g. between subgroups with and without syncopal relapses during participation in the BIOSync study or after pacing activation (with or without CLS).

12.9 Missing, unused, and spurious data

All data needed to be analyzed are pre-documented in a Statistical Analysis Plan (SAP).

During a blind review process before any pre-planned analysis, missing and spurious data, which are relevant at least for the endpoints, are identified. In case such data can't be clarified via a query management process, the Statistical Analysis Plan (SAP) is updated to avoid any bias. If appropriate, analyses will be performed both with/without spurious data.

Number of missing data are reported for each descriptive and inferential analysis in the Statistical Analysis Report (SAR) and Clinical Investigation Report (CIR), if applicable. Spurious data are commented in the Clinical Investigation Report (CIR), if applicable. Drop-outs are reported in the Statistical Analysis Report (SAR) and Clinical Investigation Report (CIR), if applicable.

Missing data will not be replaced.

12.10 Deviations from the original statistical plan

A Statistical Analysis Plan (SAP) is provided after go-life of the Clinical Data Management System (CDMS). The SAP can be updated before CDMS-freeze or closure based on a review of the data, whereby the new version is containing a change history. Any deviation from the valid SAP version with respect to inferential analyses are indicated in the Clinical Investigation Report (CIR), if applicable.

13 DATA MANAGEMENT

13.1 Methods for data entry and collection

All study-relevant medical patient data will be entered and documented pseudonymized in electronic case report forms (CRF), designed, validated and released within a Clinical Data Management System (CDMS). The established CDMS is 'iMedNet' of the vendor MedNet Solutions, Inc. As a cloud based SaaS (Software as a Service) application, that is applicable with the current versions of current internet browsers, no specific local software installation to functionality support necessary. iMedNet supports industry standards (FDA 21CFR11, HIPAA and Safe Harbor).

Use of the CDMS will allow access 24 hours 7 days a week to the study specific community (syn. study database). The PI, as well as those co-investigators to whom the PI delegates data entry and authorization of CRF, need to be trained on CDMS 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 CDMS. Once these have been validated, there will be options for adding new patients or entering new medical patient data into the CDMS.

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 has 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 at the respective section of the CIP.

13.2 Procedures used for data review, database cleaning, and issuing and resolving data queries

After data entry into the CDMS, the clinical data is automatically checked with programmed quality checks within CDMS. The CRFs will be checked against source data by clinical monitors as described in the Monitoring Plan. Errors, discrepancies, missing data, and entries out of range are resolved both automatically (CDMS) and manually (clinical monitor, clinical data manager) via 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 thereby approving 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 audit trail.

13.3 Procedures for verification, validation, and securing of electronic clinical data systems

The CDMS is hosted on a dedicated database server at the vendor MedNet Solutions, Inc. The data connections between the Internet browser of the user and the data servers of the service provider MedNet Solutions, Inc., are established with secure and certified connections. The user access and assigned roles within the CDMS is controlled and maintained by the responsible clinical data manager. Every access is automatically logged and changes of the clinical data are recorded in an independent audit trail. The CDMS is verified, validated and documented according to guidelines by BIOTRONIK and applicable regulations, e.g. FDA 21 Part 11. The user interface and the internal business logic is validated accordingly and verified during the study specific development and before the release of the CDMS for data entry.

An authenticated user account is created and maintained by BIOTRONIK for each authorized user once the user has completed the 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. The user role and rights management is documented accordingly.

13.4 Procedures to maintain and protect subject privacy

The EU GDPR guideline and related EU contractual clauses are implemented by the service provider MedNet Solutions, Inc., for CDMS and BIOTRONIK.

According to corresponding additional national laws, the patient or legal representative must declare in the Informed Consent Form (ICF) that the patient agrees to recording the patient 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 and pseudonymized. The collected data will be securely transmitted to BIOTRONIK and, if necessary, to the external assessment committees (e.g. CEC) for electronic data processing, safety reporting and analysis in compliance with the data protection law. The data will be pseudonymized at the sites before transmission, without using patient initials. To ensure traceability of patient data, but preventing unauthorized identification of individual patients, a pseudonymized patient ID is used that consists of a clinic number and a consecutive number for the patient, however no additional patient identification characteristics. All clinical data will be stored in the validated electronic system environment with adequate and documented protection against unauthorized user access.

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 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.

13.5 Methods for database locking at the start of the analysis and storage upon completion of the clinical investigation

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

For database locking, the CDMS has been prepared and a review for completeness, consistency, plausability and integrity according to the CIP and CDMP was performed:

- all expected data retrieved,
- all received data cleaned (i.e. all discrepancies have been raised and resolved for all expected data),
- all electronic data received, loaded, reconciled and cleaned,
- all coding completed and

- SAE and AE reconciliation completed.
- for final data analysis, all endpoint relevant data are checked in a blinded way by the biostatistician.

After ensuring completeness and integrity, the write access to the CDMS is limited to prevent any unplanned and non-authorized changes to the patient data. The clinical data together with the system audit trail will be securely exported from the CDMS and must be stored on a protected file server at BIOTRONIK. The export must be saved in different common and human readable file formats. Finally all user rights in the CDMS are revoked.

13.6 Procedures for data retention

Archiving of the clinical study data and the source data need to be according to the national law.

After CDMS closure, all CRF data, the audit trail and other relevant CDMS content are securely exported in human readable file formats.

All study related data and 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.

All relevant study related documents have to be stored in the Investigator Site File at the investigational sites. 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 complete archiving period.

13.7 Specified retention period

Investigational data are 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.

14 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 patients, or when the change involves only logistical or administrative aspects of the study.

15 DEVIATIONS FROM CLINICAL INVESTIGATION PLAN

15.1 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 patients 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 patients may proceed without prior approval of the sponsor and the ethics committee.

No waivers from the CIP are allowed.

15.2 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.

15.2.1 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.

15.2.2 Other deviations

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

15.2.3 Reporting

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

15.3 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.

15.4 Actions

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

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

All persons involved in a deviation have to co-operate with the sponsor in identifying and implementing the appropriate actions. Performance and implementation of these actions are documented in iMedNet and later filed in the central file and, in the case of site specific deviations, in the respective investigator site file.

Disqualification of study personnel or investigational sites is the ultimate escalation step of preventive actions. This means that in case of major deviations that seriously affect the safety and well-being of patients 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.

16 DEVICE ACCOUNTABILITY

All devices used in this clinical study carry a CE mark and will be used within their intended use. Therefore special device accountability procedures are not applicable. However, the implanted pacing systems implementing the CLS function are identifiable by a unique serial number. This number will be recorded on the relevant form in the CRF. By need or at least at the end of the study, a list with all used devices will be created.

17 STATEMENT OF COMPLIANCE

The study will be conducted in compliance with the international standard ISO 14155:2011 'Clinical investigation of devices for human subjects – Good clinical practice' and subsequent version ISO 14155:2020.

17.1 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.

17.2 Applicable international and national standards

The study will be conducted in compliance with the international standard ISO 14155 '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.

17.3 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.

17.4 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.

17.5 Patient 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.

17.6 Financing

This clinical investigation is financed by the sponsor BIOTRONIK SE & Co.KG. Contracting of investigation sites and investigators is in the responsibility of the sponsor, as mentioned in section 10.1 'Responsibility of the sponsor'. The agreement between the sponsor and the research site determines inter alia the following aspects: 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.

18 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.

18.1 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 shall 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 patients 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.

19 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 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 14155:2020 events will be classified on the basis of the definitions below.

19.1 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 and whether anticipated or unanticipated. 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

It is worth specifying that syncope, pre-syncope, heart rate and blood pressure drop during the HUTT which do not result in any consequence shall not be reported as adverse events in itself, as expected events and part of the test itself. If these events will result in any consequence of a (S)AE, the (S)AE shall be reported.

19.2 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

19.2.1 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 serious AE will be classified according to four different levels of causality. As defined in the Medical Device Coordination Group guidance (MDCG 2020-10/1), 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

Possible: the relationship with the use of the investigational device, or the relationship with procedures, 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 where 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, or the relationship with procedures, seems relevant and/or the event cannot reasonably explained by another cause.

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

The sponsor and the investigators will distinguish between the serious adverse events related to the investigational device and those related to the procedures (any procedure specific to the clinical investigation).

An adverse event can be related both to procedures and the investigational device. Complications caused by concomitant treatments not imposed by the clinical investigation plan are considered not related. Similarly, several routine diagnostic or patient management procedures are applied to patients regardless of the clinical investigation plan. If routine procedures are not imposed by the clinical investigation plan, complications caused by them are also considered not related.

In some particular cases the event may not be adequately assessed because information is insufficient or contradictory and/or the data cannot be verified or supplemented. The sponsor and the Investigators will make the maximum effort to define and categorize the event and avoid these situations. Where an investigator assessment is not available and/or the sponsor remains uncertain about classifying the serious adverse event, the sponsor should not exclude the relatedness; the event should be classified as "possible" and the reporting not be delayed.

Particular attention shall be given to the causality evaluation of unanticipated serious adverse events. The occurrence of unanticipated events related could suggest that the clinical investigation places subjects at increased risk of harm than was to be expected beforehand.

19.3 Definition of device deficiency

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

*see ISO 14155 3.19

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.

19.4 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, users, or other persons as defined by one or more of the following:

- a life-threatening illness or injury, or
- a permanent impairment of a body structure or a body function including chronic diseases, 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 including physical or mental impairment.

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 3.45

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.

19.4.1 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 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.

19.5 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

19.6 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 assessment.

*see ISO 14155 3.51

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.

19.7 Definition of serious public health threat

A serious public health threat is defined as a signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons.

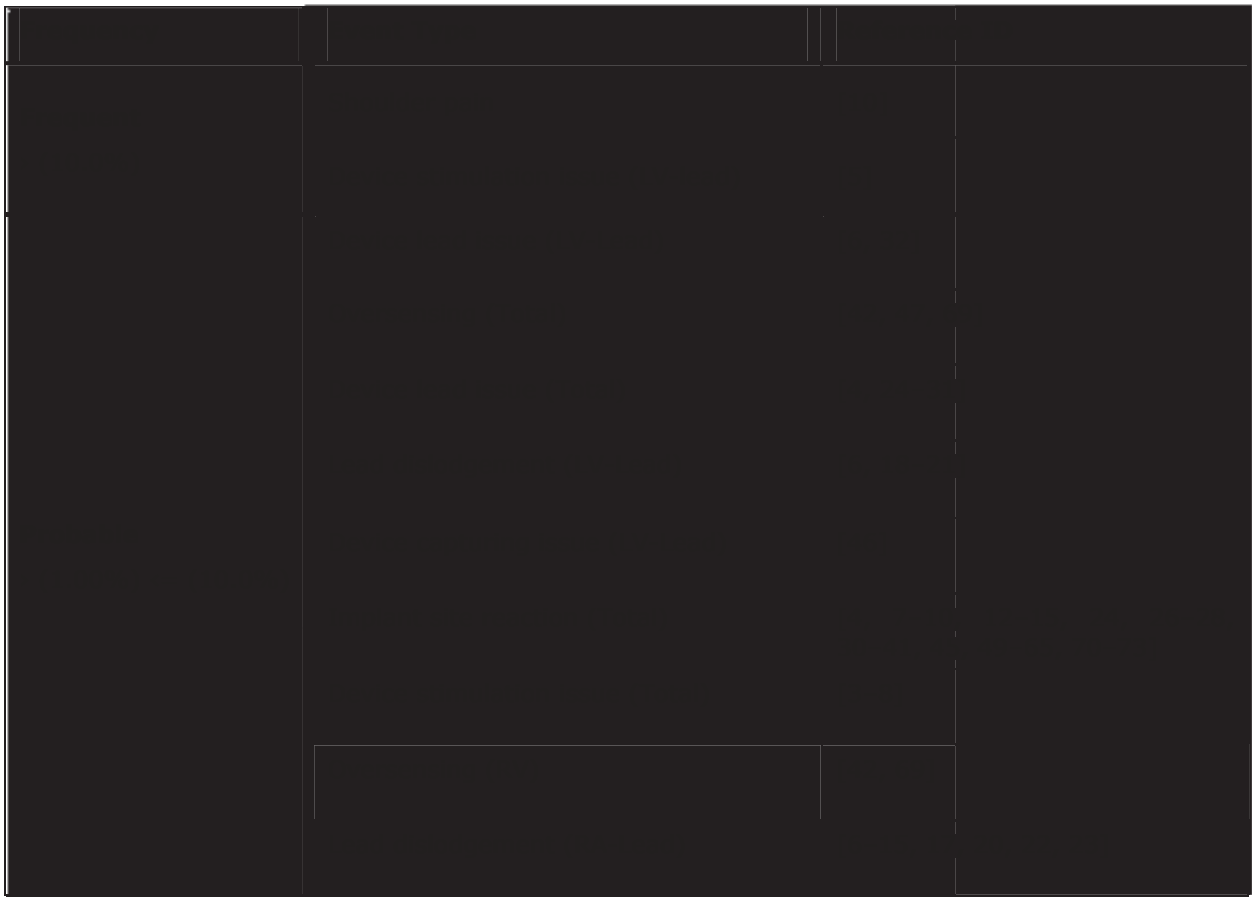
Note: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.

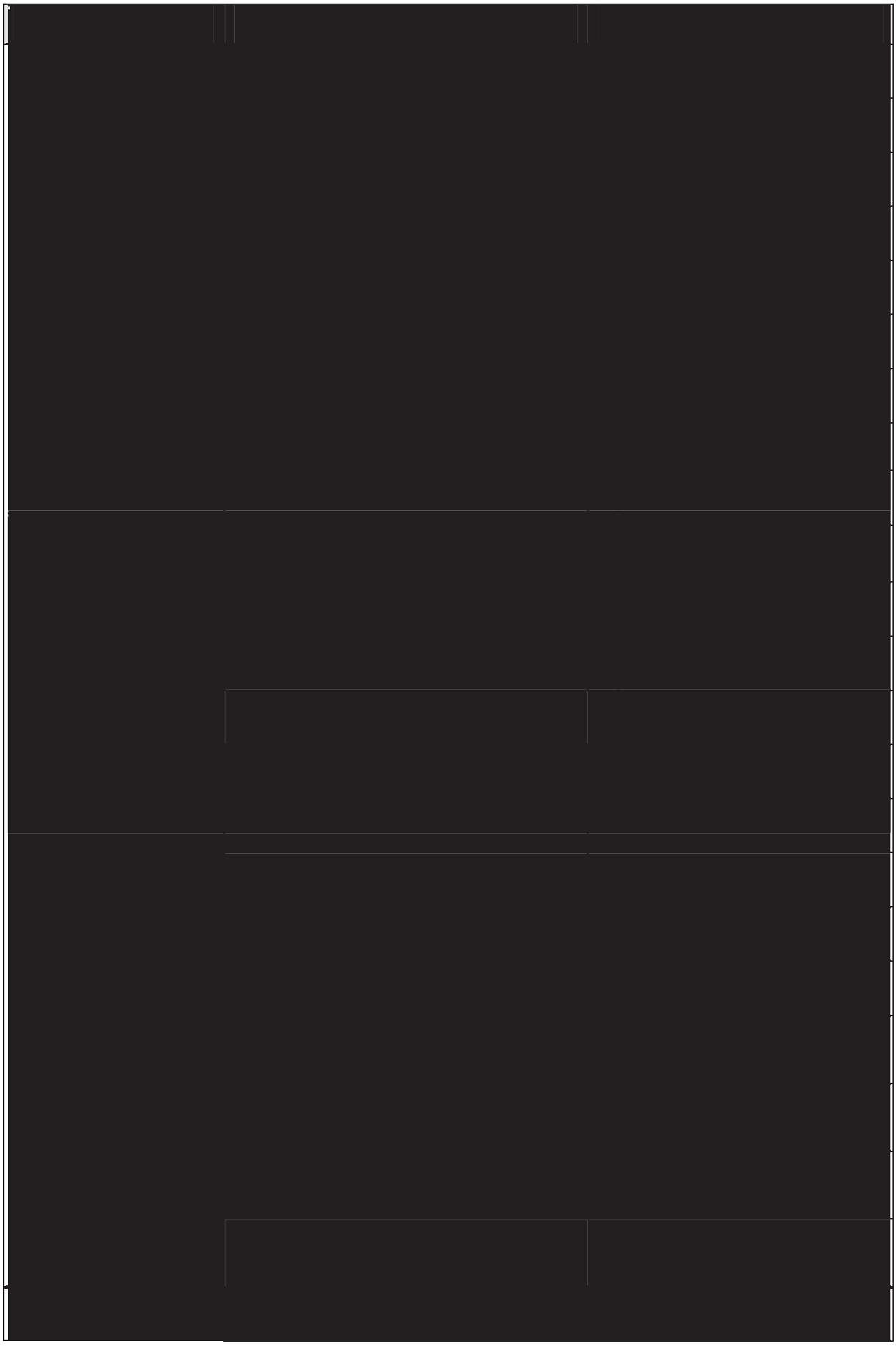
Signals from adverse events or device deficiencies that might indicate a serious health threat can be detected by either the sponsor or principal investigator but are evaluated by the sponsor.

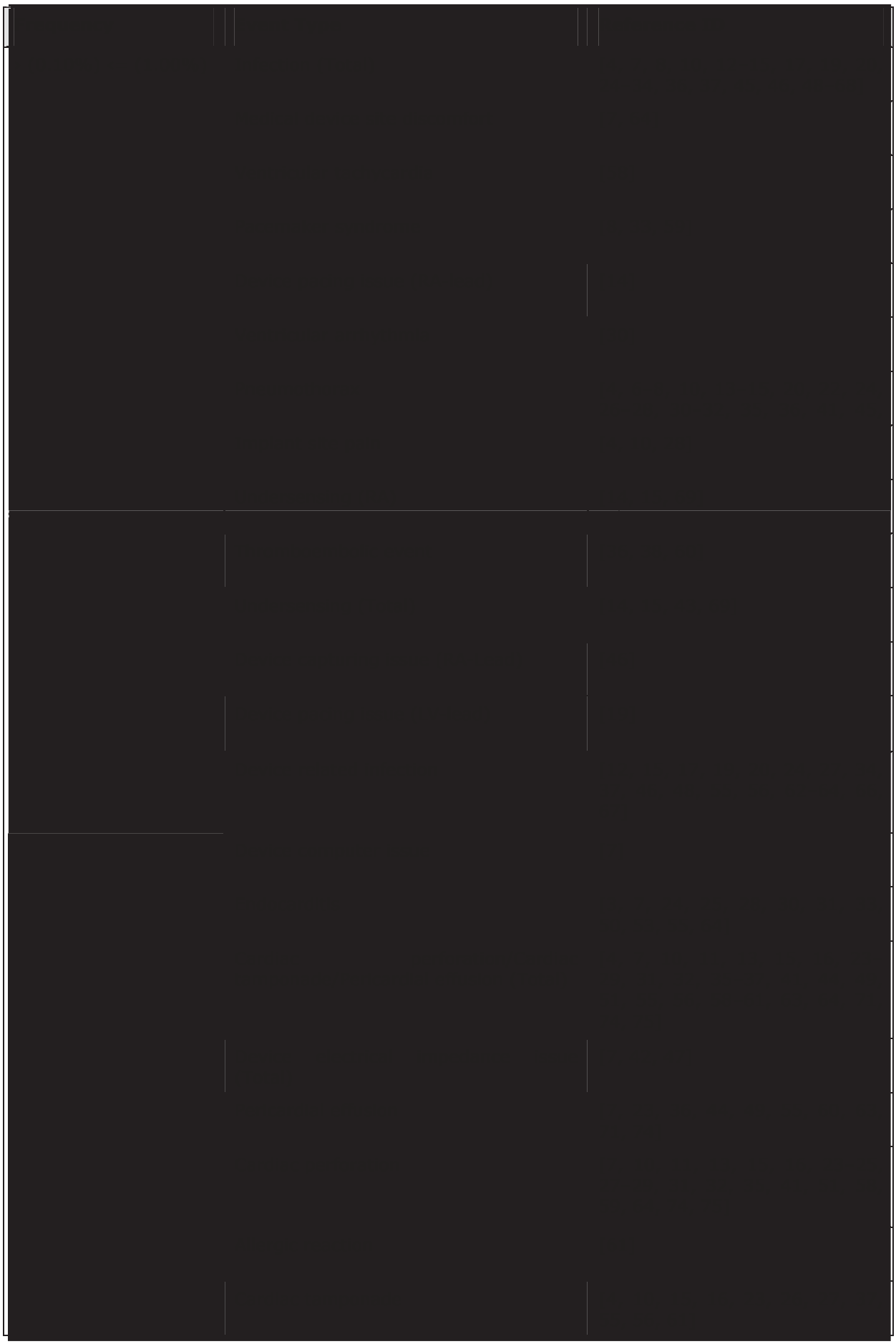
19.8 Anticipated adverse events

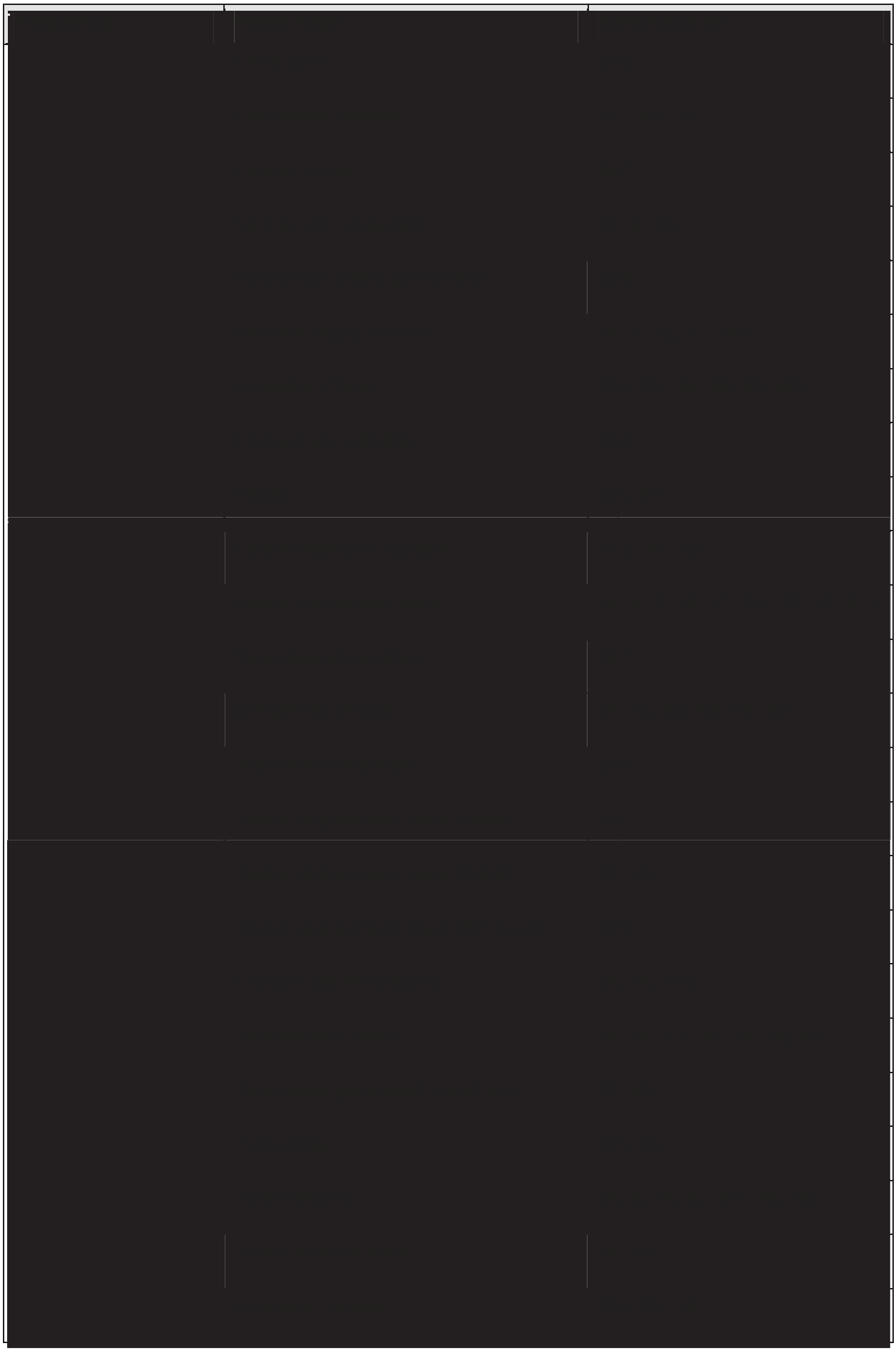
The following Adverse Events may possibly occur as medical complications of a pacemaker implantation. The most common adverse events related to the pacemaker are listed in Table 3 (list based on Clinical Complication Analysis No. 000-004-711 Rev. A, 07 Sep 2021). All references used for this chapter refer to the list at the end of this section.

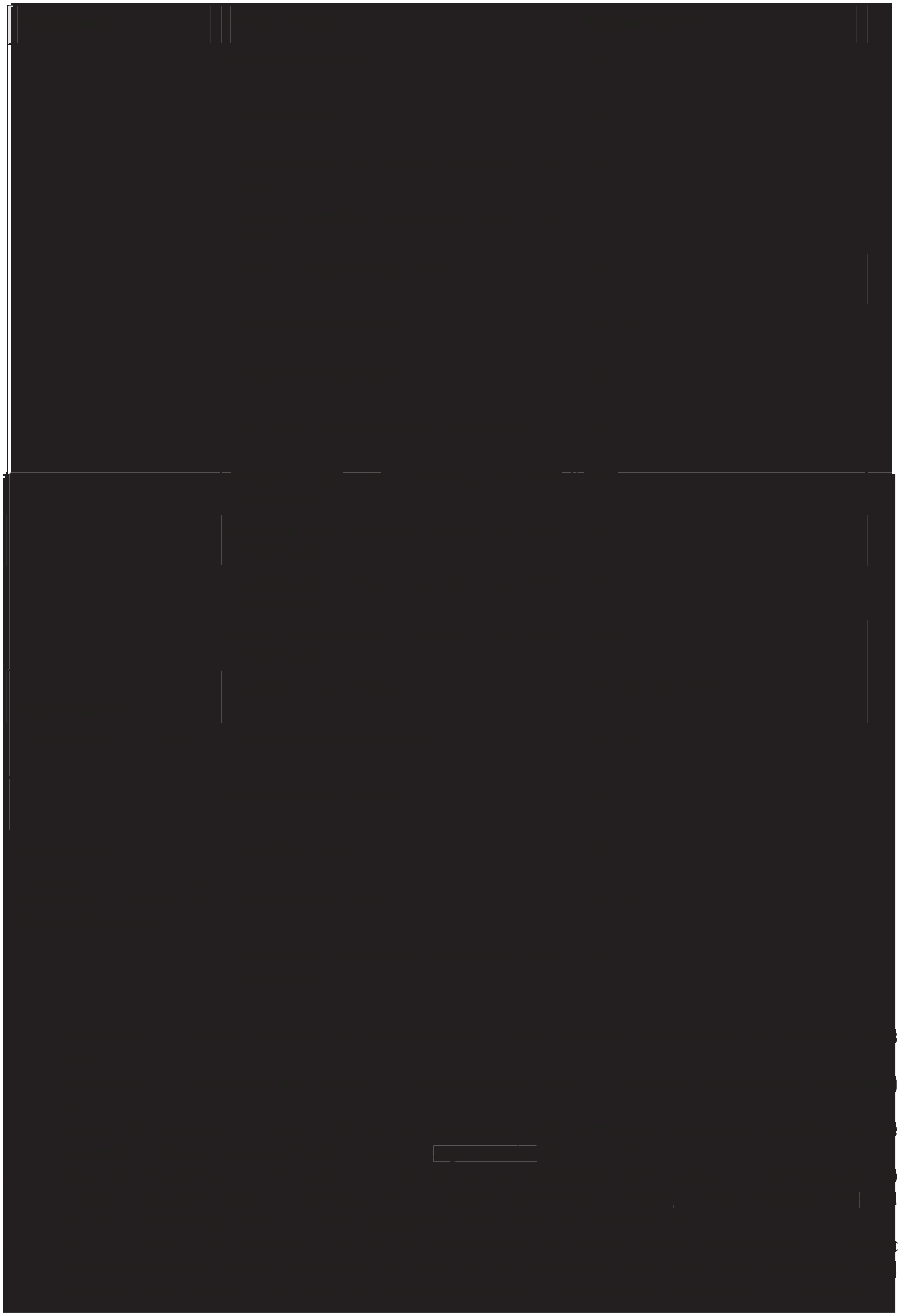
Table 3. Adverse events and probability ranges associated with pacemaker therapy

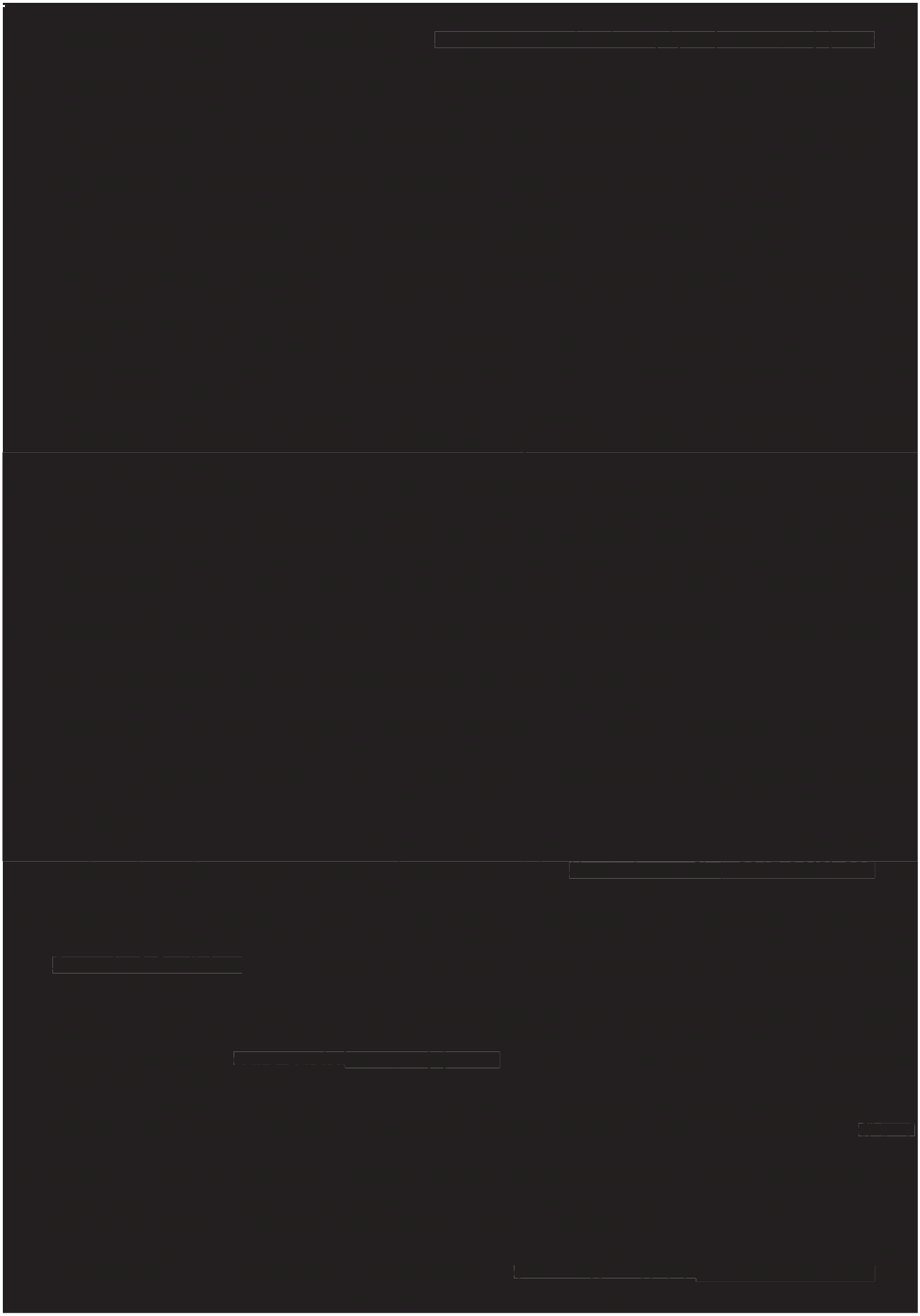












19.9 Reporting responsibilities

19.9.1 Reporting responsibilities of the investigator to sponsor

The investigator shall document all events on the respective CRF pages provided within the CDMS (iMedNet). 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 14155:2020.

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

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

The investigator must characterize each event by a single primary diagnose. The primary diagnose may describe an event consisting of several clinically recognizable features, symptoms or secondary diagnoses. Note: The observed symptoms and secondary diagnoses must be properly documented in the respective CRF.

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

19.9.2 Reporting responsibilities of the investigator to other parties

According to national and international regulations some of the involved competent authorities (CAs) and ethics committees request reporting of SAEs and DDs with SADE potential during the course of the study. Investigators have to ensure, that they fulfil these local reporting obligations given by their competent authorities and EC/IRBs.

19.9.3 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

quarterly and unanticipated serious adverse device effects (USADEs) shall be reported immediately.

19.10 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 14 days
Serious adverse event (SAE) / serious adverse device effect (SADE)	CCR BIOTRONIK SE & Co. KG: Documentation in AE-CRF	Immediately, latest within 3 days after detection[1]
Unanticipated serious adverse device effect (USADE)	CCR BIOTRONIK SE & Co. KG: Documentation in AE-CRF	Immediately, latest 24 hours 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 eficiencies to the sponsor without unjustified delay is an important part of the principal investigator's responsibilities as defined by ISO 14155:2020. 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.

19.11 Emergency contact

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

[1] If national legislation requires faster reporting the national requiremet shall be observed.

In case technical support is needed the service hotline of BIOTRONIK is available 24 hours a day. Phone: +49 (0) 30 68905-1133.

20 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. Therefore no provisions for vulnerable patients have to be arranged.

21 SUSPENSION

21.1 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/IRB

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/IRB of this decision. The investigator will also promptly inform all patients enrolled at the investigational(al) 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(al) site, the sponsor shall be informed immediately.

If the investigator decides to suspend or prematurely terminate the study at his/her site he/she will promptly inform the study sponsor, the EC/IRB and all enrolled patients of this decision.

If the EC/IRB 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 'Study 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.

21.2 Requirements for patient follow-up and continued care

In case of a study suspension, no new patients will be enrolled until the suspension has been lifted. During the suspension, follow-up and data collection will continue as per CIP. If the

suspension is due to an EC/IRB decision, additional requirements from the EC/IRB with respect to follow-up and data collection may apply.

Ongoing SADEs and SAEs of the patient will be followed in a time period of 6 weeks after premature or regular study termination of the individual patient in order to follow the outcome, clarify open questions or for collection of missing information concerning the respective SADE or SAE. Ongoing SADEs related to the investigational device will be followed over a maximum period of 6 months after study termination of the respective patient if not resolved before.

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

22 PUBLICATION POLICY

22.1 Decision for publication

The study will be registered in a publicly accessible database (e.g. clinicaltrials.gov) and the results will be made publicly available after completion of related publication activities.

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 about 18 months after analysis with sponsor approval.

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

22.2 Authorship guidelines

The first author of the publication of study results will be established according to the number of enrollments. The last author of the publication will be the [redacted] BIOTRONIK employees who meet the authorship criteria may be included in the author list.

22.3 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.

22.4 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.

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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