BIOTRONIK
excellence for life

Document Title:	Clinical Investigation Plan for the BIO|CONCEPT.Renamic Neo Study
Document Version and Date:	Version 1-0, 05-Dec-2019
ClinicalTrials.gov Identifier:	NCT04350008

Clinical Investigation Plan

for the

BIO|CONCEPT.Renamic Neo Study

Reference Number:	BA112
Version	1-0
Date of CIP:	05-Dec-2019
Investigational devices:	Renamic Neo programmer, programmer software NEO 2001.A and PK-222-L ECG cable

Director Clinical Project Management

[redacted]

BIOTRONIK SE & Co. KG
Center for Clinical Research
Woermannkehre 112359 Berlin
Germany

Date | Signature

Clinical Project Manager

[redacted]

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

Date | Signature

Director Clinical and Regulatory Affairs

[redacted]

BIOTRONIK Australia Pty. Ltd.
Level 4, Building 2, 20 Bridge St
Pymble NSW 2073
Australia

Date | Signature

Sponsor

BIOTRONIK Australia Pty. Ltd.
Level 4, Building 2, 20 Bridge St
Pymble NSW 2073
Australia

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

TABLE OF CONTENTS

1 LIST OF ABBREVIATIONS

ADE	Adverse Device Effect
AE	Adverse Event
ASADE	Anticipated Serious Adverse Device Effect
ATP	Antitachycardia Pacing
AV	Atrio-Ventricular
BP	Bipolar
CA	Competent Authority
CCR	Center for Clinical Research; BIOTRONIK SE & CO. KG study department
CDMS	Clinical Datamanagement System
CE	CE mark, a stylized 'CE' (Conformité Européenne) placed on products to signify conformance with European Union regulations
CFR	Code of Federal Regulations der USA (www.gpoaccess.gov/cfr)
CI	Coordinating Investigator
CIP	Clinical Investigation Plan
CIR	Clinical Investigation Report
CRA	Clinical Research Associate
CRF	Case Report Form
CRM	Cardiac Rhythm Management
CRT	Cardiac Resynchronization Therapy
CRT-D	Cardiac Resynchronization Therapy Defibrillator
CRT-P	Cardiac Resynchronization Therapy Pacemaker
DAL	Device Accountability Log
DD	Device Deficiency
DDD	Dual chamber with atrial and ventricular pacing, atrial and ventricular sensing, tracking and inhibition capability
DDI	Dual chamber with atrial and ventricular pacing, atrial and ventricular sensing and inhibition capability
DVI	Dual chamber with atrial and ventricular pacing, ventricular sensing and inhibition capability
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
EU	European Union
FDA	US Food and Drug Administration (www.fda.gov)
FPI	First Patient In
FSR	Funktionale Systemrisikoanalyse
FU	Follow-up visit
GCP	Good Clinical Practice

GUI	Graphical User Interface:
ICD	Implantable Cardioverter Defibrillator
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (www.ich.org)
ICM	Implantable cardiac monitor
ICMJE	International Committee of Medical Journal Editors
IPG	Implantable Pulse Generator / Pacemaker
ID	Identification Number
IEGM	Intracardiac Electrocardiogram
IFU	Instructions For Use (user manual)
iMedNet	Web-based electronic data entry (EDC) system for clinical trials provided by MedNet Solutions Inc.
ISO14155	International Organization for Standardization, norm no. 14155
ITT	Intention to Treat Analysis
LAN	Local Area Network
LPI	Last Patient In
LPO	Last Patient Out
LTE	Long Term Evolution
MAUDE	Manufacturer and User Facility Device Experience Database
MDR	Medical Device Reporting (FDA)
NHMRC	National Health and Medical Research Council
PGH	Programmer Head
PHD	Pre-hospital Discharge
PI	Principal Investigator
PNS	Peripheral Nerve Stimulation
PSA	Pacing Sensing Analyzer
QM	Quality Management
QP	Quadripolar
RF	Radio Frequency
SA	SinoAtrial
SaaS	Software as a Service
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SAS	Statistics and Analysis Software produced by SAS Institute Inc. (www.sas.com)
SDS	Source Data Sheet

SOP	Standard Operating Procedure
TGA	Therapeutic Goods Administration
UMTS	Universal Mobile Telecommunications System
USADE	Unanticipated Serious Adverse Device Effect
USB	Universal Serial Bus
VDD	Pacemaker Mode (ventricular pacing / atrial and ventricular sensing / atrial and ventricular triggering and inhibiting)
VVI	Pacemaker Mode (ventricular pacing / ventricular sensing / and inhibiting)
WLAN	Wireless LAN

2 SYNOPSIS

Title	BIO|CONCEPT.Renamic Neo
Patient population	Patients that are planned to receive or are already implanted with a programmable BIOTRONIK cardiac rhythm management (CRM) device.
Design	Observational, prospective, open, un-controlled, non-randomized, multicenter
Investigational devices	• Renamic Neo programmer • Programmer software NEO 2001.A and successor • PK-222-L ECG cable
Objectives	Collection of clinical data on the safety, performance and usability of the Renamic Neo programmer system to support regulatory approval
Endpoints	Adverse device effects and device deficiencies
Data of interest:	The following functionalities will be assessed • Pacing System Analyzer (PSA) • Sensing, pacing threshold and impedance tests with implanted device • Interrogation and programming of implanted devices • Data export and printing • General performance, safety and usability of Renamic Neo system • Performance of used accessories
Inclusion criteria	• Patient is planned for de novo implantation or already has a BIOTRONIK active, implantable device. • Patient is able to understand the nature of the study and provides written informed consent.
Exclusion criteria	• Patient is implanted with a Stratos pacemaker. • Patient is planned for implant exchange or upgrade.

	• Patient is pregnant or breast feeding. • Patient is less than 18 years old.
Study duration	April 2020 – July 2020 (approx. 3 months)
Sample size	Approximately 120 patients will be enrolled in order to collect data from 50 implantations and 100 pre-hospital discharge or follow-up cases performed with 20-30 programmer devices.
Investigational sites	Approximately 10
Follow-up scheme	For patients who are scheduled for a BIOTRONIK device implantation (except ICMs): • Enrollment • Implantation • PHD • Termination For patients who are already implanted with a BIOTRONIK active device: • Enrollment • Follow-up visit • Termination
Sponsor	BIOTRONIK Australia Pty. Ltd. Level 4, Building 2, 20 Bridge St Pymble NSW 2073 Australia

3 INTRODUCTION

A programming device is an essential user interface for active cardiac implants and as such it is an external component of the implant system.

The Renamic Neo programmer is BIOTRONIK's latest generation of programming devices. The Renamic Neo programmer system includes the programming device Renamic Neo, the programmer software NEO 2001.A and the new electrocardiogram (ECG) cable PK-222-L.

The Renamic Neo system provides communication with BIOTRONIK implantable implantable pulse generator (IPG), implantable cardioverter defibrillators (ICDs), cardiac resynchronization therapy (CRT) devices and implantable cardiac monitors (ICM) thereby constitutes a substantial external component of the implant system. The clinical functions exist within the implant, and the programmer simply provides bidirectional communication with the implant, displays implant data and parameters, and allows the programming of implant parameters during implantations and follow-ups according to the state-of-the-art concept for programming devices [1–3].

Furthermore, during implantations the integrated Pacing System Analyzer (PSA) enables the user to perform intraoperative measurements like sensing, pacing and impedance tests of the leads by connecting the leads directly to the programmer.

The overall use concept for Renamic Neo is inherited from previous BIOTRONIK programmers, particularly from the direct predecessor Renamic which gained CE-mark in September 2010 and regulatory approval in Australia in June 2011. The programmer must enable different use scenarios depending on which active implant is to be interrogated, whether the interrogation relates to implantation or to clinical follow-up, and the clinical context and patient specific requirements in which the active implant is to be used. The purpose of the development of Renamic Neo has been to provide a programmer based on up to date hardware components and to optimize the integration into the clinical workflow.

This study is designed as a pre-market study to provide clinical data and supporting evidence of the safety, performance and usability of the Renamic Neo programmer system.

4 INVESTIGATIONAL DEVICE

4.1 Summary description of the device and its intended purpose

The investigational devices used in this clinical investigation are the programmer device Renamic Neo, the programmer software NEO 2001.A and the PK-222-L ECG cable. In the following text the term 'Renamic Neo system' refers to the Renamic Neo hardware, software and the PK-222-L cable, unless otherwise stated.

Renamic Neo is a portable programmer and monitoring device that must enable the intended use of the compatible active implants. It is operated via a touch sensitive display and interrogation of the implant is achieved through a programming head (PGH) or via wandless RF telemetry. This is state-of-the art for cardiac rhythm management (CRM) programmers. Renamic Neo has an integrated PSA, which is used during implantation of BIOTRONIK implantable devices to perform intraoperative tests at the leads. In daily operation, the Renamic Neo can be operated with a power supply brick or, alternatively, with a battery. It can be custom-equipped with a mobile internet stick authorized by BIOTRONIK.

Notable enhancements to Renamic Neo with respect to the predecessor programmer Renamic include:

- Connectivity to fast mobile networks, WLAN, LAN
- Capacitive touchscreen
- High resolution display
- Smaller and lighter hardware compared to the predecessor Renamic
- Operation for a minimum of 1.5 hours through an optional internal battery
- Integration of the Pacing System Analyzer

Unlike Renamic, Renamic Neo does not have an internal printer and instead printing is possible through connection via LAN, USB or wirelessly to an external printer. Apart from the internal printer, all fundamental functionalities of Renamic are also realized in Renamic Neo.

The programmer software NEO 2001.A is highly similar in functioning to the programmer software of the predecessor Renamic. Some software features have been optimized to deliver the same overall PSA functionality and clinical performance, but with improved adaptation of usability to the preferences of the clinical user.

The PK-222-L ECG cable patient cable is used with a surface ECG to connect the ECG electrodes to a programmer from BIOTRONIK. As part of implantations and follow-ups of IPGs, ICDs, CRTs and ICMs from BIOTRONIK, the signals are transmitted via the patient cable for representation of the surface ECG on the screen. The ECG cable PK-222-L differs from the approved PK-222-EU cable in its length and the permanently mounted patient cable electrode clips.

4.2 Manufacturer

The manufacturer of the Renamic Neo system is:

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

4.3 Model name including software version and accessories

The devices undergoing clinical investigation are BIOTRONIKs Renamic Neo programmer, the programmer software NEO 2001.A and the ECG cable PK-222-L. These investigational devices have not been approved for the market release yet by a regulatory authority or notified body. Clinical data on these devices are collected to support regulatory approval.

Table 1: Investigational Devices

Model Name	Model Number
Renamic Neo including rechargeable battery	424722 445510
Programmer software NEO 2001.A and successor	449859
PK-222-L ECG cable	429747

In addition, data on the following BIOTRONIK available accessories (additional devices) may be collected, as required to support regulatory requirements (Table 2). Except for the accessory bag the listed accessories used in the scope of this clinical study are certified by the Australian Therapeutic Goods Administration (TGA).

Table 2: Available Accessories

Model Name	Model Number
Accessory bag	445749
PK-222 EU / 2.8 m ECG cable	335284
PK Electrode Clip	340293
Patient cable PK-141	353181
Patient cable PK-67-S	128085
Patient cable PK-67-L	123672
Patient cable PK-155	337358
Patient adapter PA-1-B	123751
Patient adapter PA-1-C	349723
Patient adapter PA-2	123157

4.4 Description of traceability

Every Renamic Neo programmer can be identified by its unique 8 digit serial number. Each ECG cable PK-222-L will be allocated a unique number for the use during the study. The programmer software NEO 2001.A is identifiable by its version number. The traceability is assured by recording the serial numbers or unique numbers in the device accountability log (DAL, section 15) of the clinical data management system (CDMS). This documents the shipment, receipt, transfer and/or return to the sponsor of used, unused or malfunctioned investigational devices. Device information as model name, serial/unique number, date of shipment or return and shipment destination is entered in the DAL.

Moreover, identifying numbers of investigational devices and patient ID are recorded during each use of the programmer at implantation and/or follow-up. This information is documented in the corresponding electronic case report form (CRF) in the CDMS.

Investigational devices have to be clearly visible labeled as investigational devices. Only trained BIOTRONIK personnel or trained site personal is authorized to have access and to handle investigational devices.

Malfunctioning investigational devices shall be sent back to the manufacturer. The investigator shall contact the respective sales representative in order to organize shipment.

After study termination all investigational devices have to be returned to the sponsor.

4.5 Intended purpose of the device in the study

The Renamic Neo programmer, programmer software NEO 2001.A and PK-222-L ECG cable will be used according to their intended use outlined in the respective instructions for use.

The Renamic Neo programmer system provides communication with BIOTRONIK implantable IPGs, ICDs, ICMs or CRT devices during the implantation or a follow-up. It is intended to enable normal use of the implantable products by providing a user interface for the functions of the device.

The programmer is used for the following applications:

- For verification and optimization of the therapy which is delivered by the active implant
- For support of the diagnosis of the patient status through data that is sent by the device

This is achieved by providing product properties that enable the execution of the following tasks:

- Identify supported implantable devices and retrieve, display, and print current parameter settings
- Retrieve, display, and print the recorded statistical data and episodes from the memory of the device
- Retrieve real-time IEGM data from the device
- Retrieve real-time ECG data from the ECG leads affixed to the patient
- Select the appropriate settings for the supported implantable devices by the user
- Program the supported devices with the selected parameter values
- Execute test functions (e.g. sensing, pacing threshold, and impedance test) in order to determine the internal status of the device, the connected leads, and the patient
- Initiate special programs and shocks for therapeutic purposes
- Support the implantation of leads through intraoperative measurements of the electrophysiological parameters, such as the detection of intrinsic cardiac signals, pacing threshold, lead impedance, and timing features (timing cycles) as well as to provide temporary functions of an external pacemaker
- Export data (including recordings of real-time data) of the implanted device for analysis and reporting purposes, as an automatic and user-initiated function, to a data storage unit or to a data processing system

4.6 Intended patient population and indications

The intended patient population comprises all patients that are implanted with or are intended for de novo implantation with a BIOTRONIK IPG, ICD, CRT-D (CRT-defibrillator), CRT-P (CRT-pacemaker) or ICM that can be adequately programmed and interrogated by the Renamic Neo programmer system.

Contraindications:

There are no contraindications for the Renamic Neo device itself. The following applications are contraindicated for use of the integrated pacing system analyzer (PSA):

- With AV conduction disorders:
  - Atrial single-chamber pacing
- With competing intrinsic rhythms:
  - Modes that have no sensing and inhibition function in the corresponding chamber
- With chronic atrial tachycardia as well as chronic atrial fibrillation or flutter:
  - Atrial-controlled modes (DDD, VDD)
- With poor tolerance of high ventricular rates (e.g., angina pectoris):
  - High upper rate
  - Under certain conditions: atrial-controlled modes
- With retrograde conduction after ventricular pacing:
  - Programming a short AV delay
  - Under certain conditions: DDI, DVI, or VVI mode
- Use as an external pacemaker outside of the implantation procedure

4.7 Description of the investigational device

4.7.1 Renamic Neo hardware and software

The Renamic Neo programmer system comprises the Renamic Neo hardware, software and the ECG cable PK-222-L. The functional design is highly similar to the predecessor Renamic. Some software features related to PSA functionalities and the graphical user interface (GUI) have been optimized and are described below.

The hardware consists of the Renamic Neo, the programmer head (PGH), the battery and the pacing system analyzer (PSA). Several accessories can be used with the programmer to record ECG or to conduct lead positioning checks during implantations. These include ECG cables, patient cables, electrode clips and patient adapters.

4.7.1.1 Renamic Neo hardware

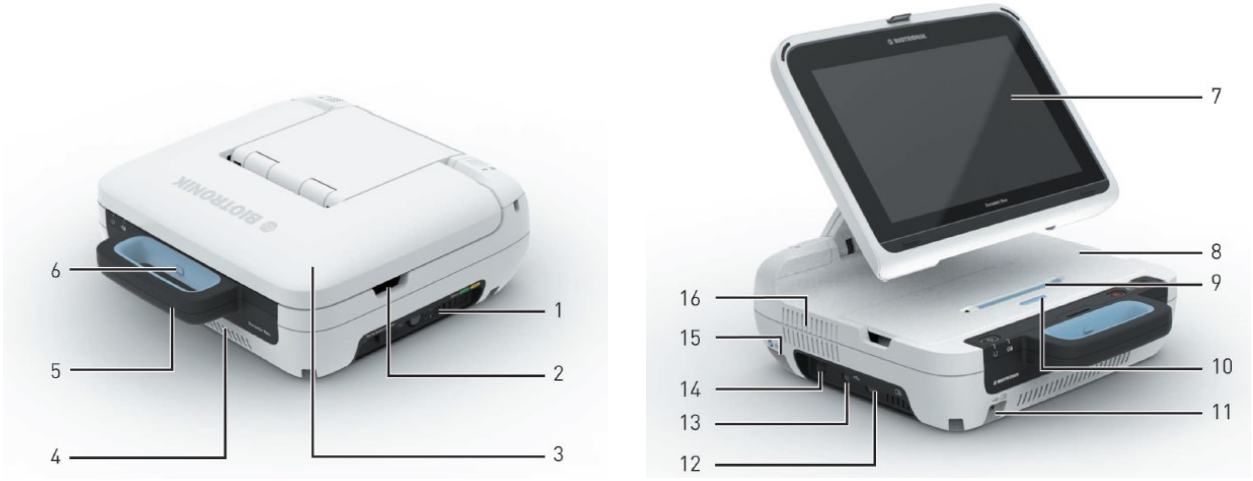

Figure 1: Description of the Renamic Neo hardware.

1. Pacing system analyzer (PSA), 2. Cable feedthrough for ECG cable, 3. Closed screen (touch screen), 4. Ventilation slots, 5. Carrying handle, 6. Screen release key, 7. Open screen (touch screen), 8. Programming head (PGH) and ECG cable compartment, 9. Stylus in pen holder, 10. Release key for the PGH/ECG power cord compartment, 11./12. USB port for connecting a printer or for exporting data to a USB flash memory stick, 13. Mini display port, 14. Ethernet port, 15. Power supply port, 16. Ventilation slots

The Renamic Neo is folded for transportation and storage (Figure 1). The monitor can be unlocked and tilted upwards to its operating position. There is a compartment under the monitor for the programming head (PGH) and the ECG cable. The ECG cable connector is located in this compartment. The PGH is permanently connected to Renamic Neo. In addition, there are two small compartments at the back of the device, to provide covered USB communication interfaces for the LTE/ UMTS-stick. The monitor provides all functions for patient-monitoring and for interrogation and programming of the implant. Additionally, buttons for activation of the emergency program of the implant are located on the upper front of the programmer: the emergency shock button (ICD only) and the safe program.

4.7.1.2 Graphical User Interface (GUI)

The programmer provides an interface for the user to the implant, and allows the user to carry-out implant interrogation, programming and implant dependent tests during implantation and during follow-up.

All available functions are displayed on the screen and can be activated by touching the screen via the supplied stylus or the user's finger (with exception of the 2 emergency program buttons discussed above). The screen is designed in such a way that certain information is displayed permanently, including the heart rate, the surface ECG and important navigation elements.

In contrast to the predecessor device the following information is displayed on the left side bar of the screen (see Figure 2):

(1) Patient, device and telemetry information

(2) Connectivity information

(3) Programmer battery indicator (% / time)

(4) Date and time always visible

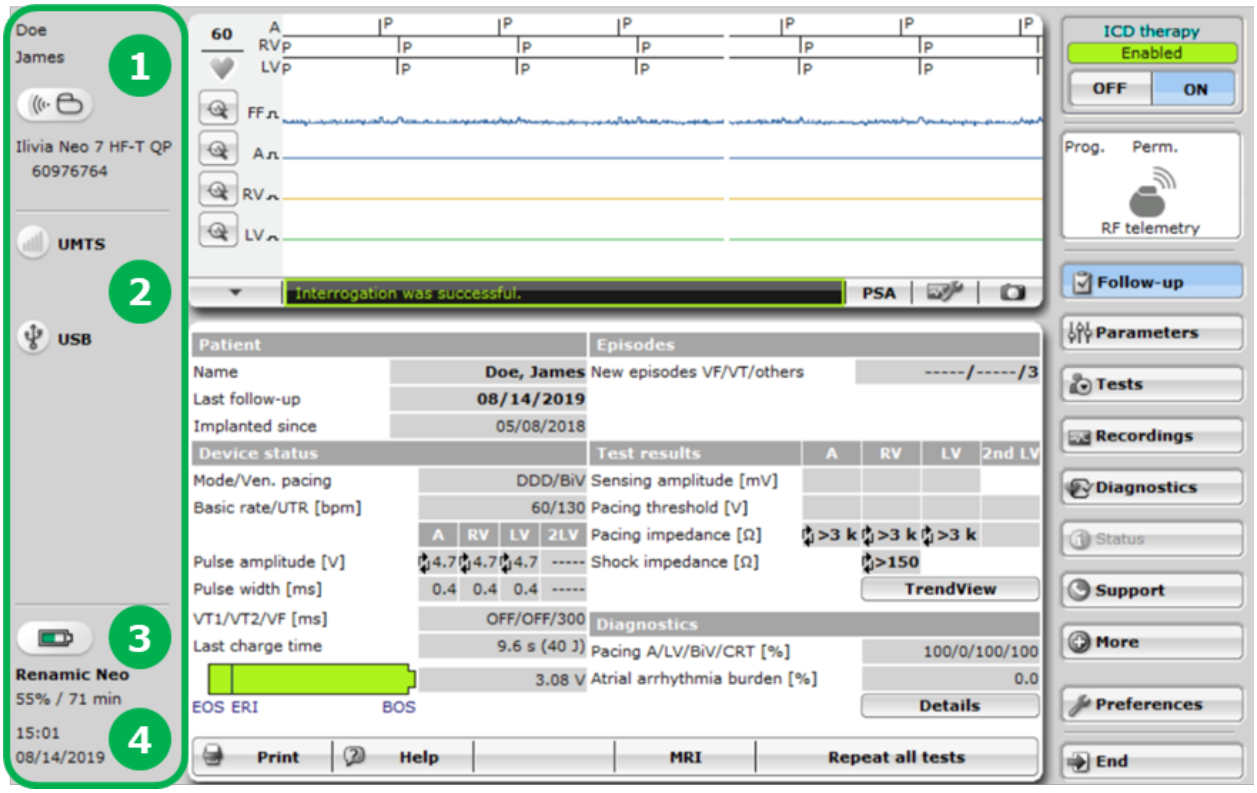

Figure 2: Screen-shot showing an example of the GUI layout.

The precise GUI layout depends on the functionality used and on the nature of the clinical use-case. In this case a 'Follow-up' screenshot is shown.

4.7.1.3 The Pacing System Analyzer

The Pacing System Analyzer (PSA) is a built-in medical diagnostic functionality to perform intraoperative measurements and tests during implantation of IPGs, ICDs and CRT-devices.

For this purpose, the PSA is directly connected to the implanted leads via patient cables with alligator clamps and adaptors.

The intra-cardiac signals from each lead are continuously acquired and displayed on the display of the Renamic Neo to allow monitoring of the patient's heart activity during the tests.

There are several changes to the predecessor device:

- The PSA hardware was fully integrated in the Renamic Neo programmer
- Polarity selection parameter was raised to the first level in the test screen. In addition, the range of selectable polarities was extended, according to the needs of quadripolar (QP) leads.
- Polarity selection allows documentation of the polarities including quadripolar measurements. Polarities are tested by the positioning of the alligator clips on the lead-connector.
- Phrenic nerve stimulation (PNS) including threshold value can be documented.
- The amplitude selection GUI has been unified with the GUI of latest implantable devices.

4.7.1.4 Interrogation of implanted devices

For programming an implanted device the interrogation of the implantable device is automatically started when the PGH is placed above the implanted device. Thus, the follow-up

session starts and all relevant parameters of the implant are transmitted to the programmer and displayed on the screen (Figure 2). The clinical user can activate various functions on request – the range of functions available depends upon the range of functions of the respective implant.

Functions may include:

- Interrogation, display, modification and storage of the parameters of the implant
- Analysis of the real-time IEGM or marker channel
- Performing tests (e.g. threshold and impedance tests)
- Display of episodes and statistics
- Display and change of patient data
- Print documentation of the follow-up care

The follow-up procedures are archived automatically in Renamic Neo, and as such follow-up data is saved on the programming device and can be displayed, printed (externally), saved on a storage media or sent to other systems at any time. This data includes:

- Program parameters at the beginning and end of follow-up
- Results of the tests performed during follow-up
- Patient data

IEGM-episodes that were recorded by the implant are not automatically transferred to Renamic Neo due to their size.

4.7.2 PK-222-L ECG cable

The PK-222-L ECG cable is used to transmit signals from the ECG electrode to the BIOTRONIK programmer in order to display surface ECGs on the programmer screen.

The PK-222-L ECG cable is longer (4 m) than its predecessor and has four color-coded and permanently mounted patient cable electrode clips on the patient side for extremity derivations according to Einthoven. They are compatible with adhesive and clamp electrodes with snap connectors.

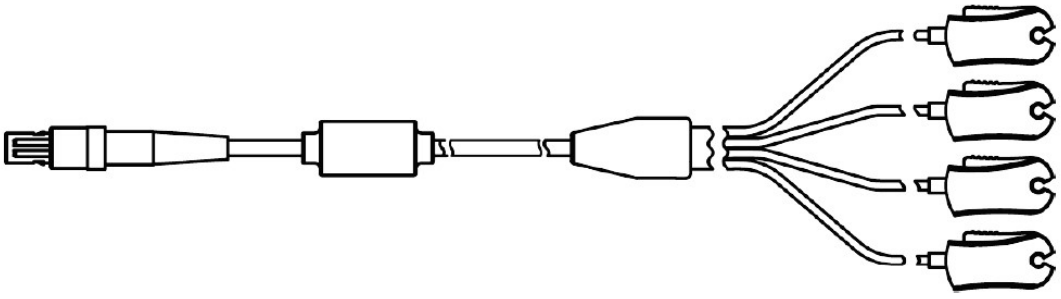

Figure 3: ECG cable PK-222-L

The assignment of the four color-coded patient cable electrode clips for extremity derivations according to Einthoven is as follows:

Extremity	PK-222-L ECG cable
Right arm	R / red
Left arm	L / yellow
Left leg	F / green
Right leg	N / black

4.8 Summary of training and experience needs

The Renamic Neo system is an external medical device intended for clinical staff members who are familiar with the use of programmers during implantations and follow-ups of cardiac implants. The user must be familiar with the Renamic Neo system including the new features. Therefore, study team members will be trained by a qualified representative of the sponsor on the Renamic Neo system.

The physician must be familiar with the associated risks and complications. The handling and use instructions are described in the respective Technical Manuals (instructions for use) for the Renamic Neo programmer, the software NEO 2001.A and the PK-222-L ECG cable[4–6].

The interrogation and programming of BIOTRONIK implantable devices by the Renamic Neo system shall only be done by an appropriately trained investigator. All study team members must be adequately trained on the study procedures.

The analysis of interrogated data, conducted tests and the assessment of the implant programming has to be performed by qualified clinical staff.

4.8.1 Description of medical and surgical procedures

The Renamic Neo system will be used during implantations, pre-hospital discharges (PHDs) and follow-ups according to clinical routine and current instructions for use. This includes the recording of surface ECGs and the use of the PSA to test for correct lead positioning during implantations by connecting the programmer to the implanted leads.

5 JUSTIFICATION FOR THE DESIGN OF THE CLINICAL INVESTIGATION

5.1 Pre-clinical data

No pre-clinical data are available for the Renamic Neo programmer, software or PK-222-L cable. Animal tests were not performed for the Renamic Neo programmer as it is an external device. The most relevant verification and validation tests for the Renamic Neo system are described in the Investigator's Brochure[7]. Investigational devices will not be provided to study sites until all tests are successfully completed.

5.2 Clinical data

For the Renamic Neo system, no clinical data are available yet.

The preceding programmer Renamic has been used in many BIOTRONIK sponsored clinical studies, e.g.

- QP ExCELs (NCT03155724)[8]
- Eluna Family Sentus BP Master Study (NCT02059629)[9]
- Matrix (NCT01774357)[10]
- BIO|MASTER.Ilivia / Plexa Family (NCT02774616)[11]
- BIO|MASTER.BioMonitor 2 (NCT02565238)[12]

Renamic was granted CE approval in Sep 2010 and was predominantly used in any BIOTRONIK study starting from January 2015 onwards that supported regulatory approval. Renamic was not explicitly investigated in these studies, but the positive results of these studies imply a correct and safe functioning of this programmer generation. As the functioning of the Renamic Neo is highly similar to that of the Renamic it is expected that the complication rate will be very low.

5.3 Justification

The main objective of this study is to provide evidence for the clinical safety, performance and usability of the Renamic Neo programming device including software and PK-222-L ECG cable.

The study is designed in a use case centric approach, i.e. it follows the usage of Renamic Neo programmer system and not the individual patients, so that a sufficient number of use cases is collected that allows for the detection of possible adverse device effects and device deficiencies caused by the programmer.

Patients will stay in the study only for implantation and PHD or follow-up and are terminated directly afterwards as ADEs and DDs related to the programmer are expected to occur only during the use of the programmer.

As the Renamic Neo system will be used for the first time in clinical routine, a significant number of use cases from implantation – given that the PSA module might be used – and follow-ups shall be included in this study. Please refer to section 11 for the justification of the sample size calculation.

Approximately 10 clinics with 2-3 Renamic Neo systems each are planned to participate. The multi-centric design will ensure that different environments in which the programmer is placed and used as well as potential hospital specific differences in programmer handling and usage are covered. While just several sites would be sufficient for that purpose, approximately 10 sites will be involved in order to realize a fast study completion. Depending on the special requirements of the sites to use the programmer at different locations at the same time, sites will receive 2-3 Renamic Neo device systems respectively. This results in an approximate number of 20-30 investigational devices.

To cover a broad range of programmer functionalities the device will be used during implantations including PSA usage, if applicable, and follow-up visits. Furthermore, the

enrollment of patients will not be restricted to any subgroup or indication in order to cover use cases for the different CRM devices.

The endpoints adverse device effects and device deficiencies are selected to analyze the safety of the Renamic Neo system and to identify possible residual risks of the programmer. Based on rare observations of events caused by the programming device in the past, only a small number of events are expected. Therefore, no power calculation and no hypothesis for the event-free rate can be provided.

Additional data from implantation and follow-up visits will be collected to confirm the performance and usability of the Renamic Neo system.

6 RISKS AND BENEFITS OF THE DEVICE AND CLINICAL INVESTIGATION

6.1 Anticipated clinical benefits

The Renamic Neo device is a state of the art programming device that is designed to integrate into the clinical workflow in order to make the clinical routine more efficient. Apart from this potentially better workflow there will be no benefit for patients that participate in this clinical study.

6.2 Anticipated risks

6.2.1 Anticipated adverse device effects

Adverse device effects anticipated for the use of the Renamic Neo system are described in section 18.7. Since no additional procedures outside the clinical routine are required in this study, no further study-specific adverse device effects (ADEs) are anticipated.

6.2.2 Residual risks associated with the device

In principle, technical failures in the programmer due to transmission errors, random component failures, software malfunction, or other events that could lead to harm, cannot be ruled out completely. These are expected but unlikely events.

Instructions for use to support correct use and to avoid use error are provided, but user errors cannot be prevented completely. Potential harm related to technical failure of the programmer or use errors have been evaluated [13] and are listed below:

- Nausea / sickness / slight dizziness
- Cardiac arrest and tachycardia
- Prolonged undesired medical condition, anesthesia or psychological stress
- Acute and serious heart failure
- Thermal tissue load
- Misdiagnosis and repeated invasive intervention
- Infection
- Asystole

There may be other risks associated with the devices that are currently unforeseeable.

6.2.3 Risk associated with participation in the study

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

There are no study-related procedures outside the clinical routine care planned. PSA measurement procedures do not differ from the procedure with the predecessor Renamic PSA module. Therefore, no additional risks or burdens are expected to derive from participating in the study.

6.2.4 Possible interactions with concomitant medical treatments

The use of the Renamic Neo is not expected to interfere with concomitant medication or other medical treatment.

The individual cardiovascular medication may have to be adapted to the patient's needs independent of the Renamic Neo device.

6.3 Steps to control or mitigate the risks

Risks related to the design, the technical characteristics, and the handling of the Renamic Neo programmer as mentioned above and in section 18.7 have been reduced by appropriate risk control measures defined in the respective BIOTRONIK Function System Risk Analysis (FSR) [13].

They are minimized through the compliance with the technical manual and special training of the clinical site staff on the Renamic Neo by BIOTRONIK staff, compliance with this clinical investigation plan and technical procedures, close monitoring of the patient's physiologic status during the use of the Renamic Neo, and by promptly supplying BIOTRONIK with all pertinent information required by this clinical investigation plan.

National data protections laws and the European Regulation (EU) 2016/679 must be followed. 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. Access to investigational devices is restriced (see section 15) Nevertheless, a residual risk remains (see section 6.2.2).

6.4 Risk-to-benefit rationale

Patients participating in the BIO|CONCEPT.Renamic Neo study are scheduled for an implantation of an IPG, ICD, CRT device or ICM from BIOTRONIK or already have such a BIOTRONIK device implanted. Programming devices are essential to adapt the implants to the patient's needs and to obtain data about device function and physiologic data. By participating in this study patients have no direct benefits, but they contribute to the medical progress which may benefit other patients in the future. The advanced features and properties (e.g. internal battery, less weight) of the Renamic Neo system may improve the clinical workflow.

The use of programmers to interrogate, and program IPGs, ICDs, CRT-devices and ICMs is state-of-the-art. Programmer-related complications are rare. The risks of the use of Renamic Neo system do not exceed the levels expected and acknowledged for programmers, and are clearly outweighed by the possible benefits.

The Renamic Neo system therefore has a favorable benefit-risk profile - the benefit-risk profile according to current knowledge and the state-of-the-art in the affected medical areas and according to available medical alternatives is positive.

7 OBJECTIVES AND HYPOTHESES

7.1 Objectives

This study is designed as a pre-market clinical study to provide evidence on the safety, performance and usability of the Renamic Neo programmer hardware, software and ECG cable PK-222-L to support regulatory approval, with a focus on requirements of the European Medical Device Regulation (MDR). The study is also intended to identify and evaluate residual risks associated with the use of the Renamic Neo programmer system that remained unrevealed even after risk analysis, risk mitigation and completed validation of the device. The results will be used to update the clinical evaluation of the devices.

7.2 Endpoints and hypotheses

7.2.1 Primary endpoint and hypotheses

There is no pre-specified statistical hypothesis and thus no primary endpoint. All analyses are explorative only.

7.2.2 Endpoints

In this study the number of adverse device effects and device deficiencies (DD) that occur in patients, users or other persons will be evaluated. Definitions are given in section 18. The investigator is asked to report any ADEs or DD that occurred during implantations and follow-ups.

- Number of adverse device Effects / device deficiencies per number of implantations
- Number of adverse device Effects / device deficiencies and per number of follow-up cases

ADEs will be adjudicated by an internal adjudication board, whereby the seriousness and device relatedness will be re-examined. If any amply documented external physical influence (e.g. accident, general power blackout) or medical AE caused the ADE, it does not contribute to this endpoint.

[redacted]

7.4 Safety assessments

Adverse events, adverse device effects and device deficiencies will be assessed in this clinical study as described in section 18 and according to the SOPs of the Sponsor. Steps to mitigate and control risks and anticipated adverse device effects as described in section 6.2 are addressed in section 6.3.

7.5 Further data of interest

General information

- Patient demographics and medical history
- Implant type and model, all other implanted devices
- Lead model and programmer software version

During implantation and follow-ups additional data on safety, performance and usability of the Renamic Neo system and accessories will be collected.

- Use and assessment of PSA functionality (sensing, pacing and impedance tests)
- Success of adequate programming of the implant

- Evaluation of interrogation of the implant including RF telemetry
- Overall assessment of device hardware or software performance including battery use
- Data export evaluation (used connectivity, destination, printing)
- Export of programmer data export files that document the performed use case for evaluation at the sponsor
- Information on additionally used accessories or other implanted cardiac devices

8 DESIGN OF THE CLINICAL INVESTIGATION

8.1 General considerations

8.1.1 Type of clinical investigation

The study is designed as an observational, prospective, open, non-randomized, non-controlled, multicenter study that is planned to be conducted in Australia and New Zealand.

8.1.2 Measures taken to minimize or avoid bias

The study will be conducted according to BIOTRONIK's internal Standard Operating Procedures to minimize and avoid potential bias.

The study does not require randomization or blinding as it does not require a control group.

It will be conducted at up to 10 sites to avoid a hospital-specific bias caused by the specific hospital environment or the programmer user. A maximum number of 30 programmer use cases (implantations and FUs) per site is defined to avoid site specific bias in case of high enrollment rates of single sites. Exemptions will be communicated in written form in case enrollment is too slow.

Furthermore, the number of implantations and follow-ups for a specific implant type is defined for the whole study to avoid an unbalanced usage of specific, implant related programmer functions. The 50 implantation and 100 follow-up (including PHD) cases should be distributed as follows:

- IPG, ICD: ~15 implantations and ~20 follow-up cases for each
- ICM: ~20 follow-up cases
- CRT-D /-P: ~20 implantations and ~40 follow-up cases for both combined

As no PSA measurements will be performed for ICMs no implantation cases or PHDs shall be performed for ICMs, but only follow-up cases.

A survey for implantation and follow-up numbers for each implant type is implemented in the iMedNet system. The sponsor will immediately inform all sites whenever the required number of a certain implant type has been reached.

8.1.3 Selection of measurements for endpoints

For the defined endpoints the number of adverse device effects and device deficiencies will be determined for implantation cases and for follow-up cases separately as different programmer features are used for both use case types. The Renamic Neo system shall be used according to clinical routine, therefore no study specific measurements are planned. The measurements for Renamic Neo performance will be focused but not restricted to new features compared to its predecessor Renamic as for the Renamic sufficient experience in clinical use is available.

8.1.4 Methods

All clinical procedures in this study will be performed according to clinical routine. Detailed information on the use of the Renamic Neo system can be found in the Technical Manuals and other study documents. The time schedule and all parameter and measurements that are recorded during the study are described in section 9.1. The corresponding data will be documented in the respective CRFs at the following points in time:

For patients who are scheduled for a BIOTRONIK active device implantation	For patients who are already implanted with a BIOTRONIK active device:
• Enrollment/ baseline • Implantation • Pre-hospital discharge • Termination	• Enrollment/ baseline • Follow-up • Termination

The following events shall be documented at any time

- Adverse events (including device related adverse events in users and other persons)
- Device deficiencies

8.1.4.1 Source Data Verification

Source data, e.g. medical records, for data entered in the CRFs have to be available for source data verification by the sponsor's clinical monitor. Patients have to consent to the use of their medical data prior to enrollment by signing the informed consent form.

Source data sheets (SDS) shall be completed and signed by authorized clinical study team members if the data entered in the CRFs is not documented elsewhere as source data. This includes the assessments of the Renamic Neo system during implantation and follow-ups.

8.1.4.2 Device Log

Information on implanted devices (type and model), leads and used accessories shall be entered in the device log

- at baseline, if patient is enrolled for follow-up
- at implantation, if patient is enrolled for device implantation

8.1.5 Equipment to be used for the assessment of variables

The following equipment is used during the study to collect data in combination with the Renamic Neo or as optional accessories:

Cables and adapters:

- PK-222 EU / 2.8 m ECG cable
- PK Electrode Clip
- Patient cable PK-141
- Patient cable PK-67-S
- Patient cable PK-67-L
- Patient cable PK-155
- Patient adapter PA-1-B
- Patient adapter PA-1-C
- Patient adapter PA-2

All devices are used within their intended purpose.

8.1.6 Replacement of subjects

Patients are enrolled in the study only for the time of study related measurements during implantation and PHD or follow-up. Patients that drop out before any study related use of the Renamic Neo system will be replaced. No drop-out rate was defined (see section 11.4).

8.2 Used devices and comparators

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

The Renamic Neo system is an external device. During implant interrogation the programmer head (PGH) might have contact to the intact skin when the PGH is placed above the implant site. For PSA measurements during implantation the leads are connected to the Renamic Neo via patient cables and alligator clamps but there will be no direct exposure to the Renamic Neo device. For surface ECGs the ECG cable PK-222-L will connect the ECG electrodes to the programmer and might have contact with the intact skin of the patient.

No comparator is used in this study.

8.2.2 Justification of the choice of comparators

Not applicable.

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

See section 8.1.5 for medical device accessories that are used during this clinical study. No medication is required by this study protocol.

8.2.4 Number of investigational devices to be used and a justification

In this study 20-30 Renamic Neo programmers including software NEO 2001.A will be used at different investigational sites. The sample size calculation (see section 11.2) is based on the number of use cases at implantation and at PHDs plus follow-ups and not on the number of devices as unforeseen safety issues are expected to be rather related to software problems than to the Renamic Neo hardware.

8.3 Subjects

8.3.1 Description of patient population

The patient population comprises all patients with BIOTRONIK CRM devices that can communicate with the Renamic Neo programmer. These are patients with an indication for a IPG, ICD, CRT or ICM device according to current clinical practice who are implanted with or are intended to be implanted with a respective BIOTRONIK device according to the investigator's decision. Therefore the patient population in the study represents a diverse patient population and use cases that are expected for the Renamic Neo system. Patients with a Stratos pacemaker are excluded as this device model is no longer supported by the Renamic Neo system. Patients who are planned for a device exchange or device upgrade are excluded from this study as polarity measurements of the newer quadripolar leads are planned in the study and these are most likely not implanted in patients with older implants.

8.3.2 Inclusion criteria

To be eligible for the participation in the BIO|CONCEPT.Renamic Neo study, patients must fulfill the following inclusion criteria at the time of enrollment:

- Patient is planned for de novo implantation or already has a BIOTRONIK active, implantable device
- Patient is able to understand the nature of the study and provides written informed consent.

8.3.3 Exclusion criteria

The following exclusion criteria must not be fulfilled at enrollment:

- Patient is implanted with a Stratos pacemaker.
- Patient is planned for implant exchange or upgrade.
- Patient is pregnant or breast feeding.
- Patient is less than 18 years old.

Note: The inclusion and exclusion criteria apply at enrollment.

8.3.4 Screening failure

No screening procedure is planned for this study.

8.3.5 Drop-out criteria

8.3.5.1 Withdrawal of patient consent

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

8.3.5.2 Patient is lost to follow-up

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

8.3.5.3 Drop-out according to protocol

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

Violation of inclusion or exclusion criteria is detected before any measurements with the Renamic Neo system were performed, for example, if the patient does not receive an implant device. This shall be considered as premature termination and has to be documented in the termination form.

8.3.5.4 Patient death

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

8.3.6 Point of enrollment and study termination

Point of enrollment is the date of signature of the informed consent form by the patient.

Date of regular termination for each patient is the date of discharge from the index hospitalization for implantation cases or the date of follow-up after follow-up completion for follow-up cases.

In case of premature termination the following rules apply:

- In case of withdrawal of a patient's consent, the date of study termination shall be the date of withdrawal of consent.
- If patient is lost to follow-up, the date of study termination shall be the day of the last contact of the site study team (e.g. investigator or study nurse) with the patient
- If the implantation is not performed succesfully due to any reasons the date of study termination shall be the date of the unsuccessful implantation attempt if another attempt is not planned within the following 2 weeks.
- In case of patient death, the date of study termination shall be the date of death.
- In case the patient is terminated prior to study specific procedures because a violation of an inclusion/exclusion criterion was discovered the date when the violation was discovered shall be the date of termination.

Study related procedures and documentation shall end at the day of study termination for the respective patient. However, all adverse device effects will be followed for up to 2 weeks after study termination of the respective patient.

[redacted]

9 STUDY PROCEDURES

9.1 Overview

Patients will be enrolled either for implantation including subsequent pre-hospital discharge or for a follow-up visit only. ICM patients will be included for follow-ups only. As the total study duration is planned for only 3 months different patients will be included for implantation and for follow-up. Patients that have been enrolled in the study and were terminated shall not be included a second time in the study.

All study related procedures performed (Table 3) have to be documented in the CRFs.

Table 3: Overview of study procedures

Investigations	Enrollment / Baseline	For patients enrolled before implantation		For patients enrolled after implantation
		Implantation	Pre-hospital discharge	Follow-up
Patient informed consent	x			
Verification of in- and exclusion criteria	x			
Demographics and medical history	x			
Information on implanted IPG, ICD, CRT or ICM, leads (device log)	x*	x		
PSA measurements and evaluation		x		
Device based measurements and evaluation, if applicable		x	x	x
Evaluation of implant interrogation and programming functionality		x	x	x
General assessment of Renamic Neo hardware and software		x	x	x
Evaluation of usability of Renamic Neo system		x	x	x
Data export (connectivity, printing)		x	x	x
Data export of use case data for evaluation at sponsor		x	x	x
Used accessories (including entry in device log)		x	x	x
Battery usage		x	x	x
Adverse event and device deficiency reporting	x	x	x	x
Concomitant medication	x[1]	x[1]	x[1]	x[1]
Regular termination			x	x

x point in time of study procedure depends if patient is enrolled for implantation use case (includes PHD) or for follow-up use case.

x* point in time for follow-up cases

x[1] only if related to an AE

All Renamic Neo programmer systems at a given site should be used roughly for the same number of use cases. Further measures to avoid bias are described in section 8.1.2. This

includes the distribution of implantation and follow-up cases between implant types. The use of the ECG cable PK-222-L is optional but use and evaluation have to be documented in the respective CRFs.

9.2 Enrollment / Baseline visit (all patients)

Prior to enrollment into the clinical investigation the investigator has to verify the eligibility of the patient based on all inclusion and exclusion criteria (see section 8.3.2 and section 8.3.3.). The informed consent has to be signed and dated by the patient and the investigator. The date of patient enrollment is defined as the date of patient signature.

The informed consent process has to be documented in the subject's medical records and the subject 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 the sponsor's monitor.

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

- Version number of the ICF
- Confirmation that patient met all inclusion and none of the exclusion criteria
- Confirmation that the patient dated and signed the patient ICF personally or an independent witness dated and signed the ICF since the patient is unable to write
- Date of patient signature on the informed consent form
- Date of investigator signature on the informed consent form

After a subject has been enrolled, the following data needs to be collected and entered in the baseline evaluation or device log CRF.

- Date of baseline assessment
- Demographic characteristics
- Medical history
- Enrollment for implantation case or follow-up case
- Only for follow-up patients at baseline: implant type and model and implanted leads in the device log
- Any adverse event or device deficiency that occurs after enrollment. Adhere to the reporting timelines listed in section 18.9.

9.3 Implantation (only patients enrolled for implantation and PHD cases, excluding ICMs)

The device implantation has to be completed within 2 weeks after enrollment. Otherwise the patient's study participation will be terminated. Patients with ICMs shall not be enrolled for implantation cases and PHDs.

The device will be implanted according to clinical routine and as described in the respective IFU. The PSA functionality of the Renamic Neo shall be used for lead measurements.

9.3.1 Documentation and procedures during implantation

- Document serial number of investigational devices used (programmer, and ECG cable PK-222-L if applicable) and version of Renamic Neo software.
- Document implant type and model, as well as leads and used accessories in the device log.
- Complete implantation SDS and enter data in the iMedNet EDC database in the implantation CRF

- Document any adverse event or device deficiency that occurs during the procedure in the respective CRFs. Adhere to the reporting timelines listed in section 18.9.
- The following procedures shall be performed in the study. Perform intraoperative measurements at leads with the PSA of the Renamic Neo system according to clinical routine. The used functionalities shall be assessed and documented. These include if applicable for the device type:
  - Sensing, pacing threshold and impedance tests
    - Documentation on device mode used for PSA measurements (1, 2 or 3 chambers)
    - Quadripolar measurement (only for QP lead)
    - Documentation of tested polarities, if applicable
  - Phrenic Nerve Stimulation (PNS) test and threshold documentation, if applicable
  - Documentation of RF surgical equipment if used during PSA measurements
  - Documentation of burst, if applicable
  - Evaluation of accuracy of PSA measurements compared to results of implant measurements (see below)
- Perform according to clinical routine, document and assess functionalities used with the implanted device. These include for all CRM devices if applicable for the device type:
  - Sensing, pacing threshold and impedance tests
  - LV VectorOpt (only for QP leads)
  - Documentation of PNS test if performed
- Evaluate if device interrogation (including RF telemetry) and adequate programming was successful
- Assess programmable parameters (e.g. programmer preferences and PSA)
- Export programmer data files for evaluation at sponsor
- Transmit clinical documentation with the programmer for own usage and assess (data export and / or printing)
- Mobile usage of programmer with battery

9.4 Pre-hospital discharge (only patients enrolled for implantation and PHD cases)

Patients enrolled for implantation cases will have a pre-hospital discharge (PHD) in most cases which will count as follow-up case.

Device interrogation and programming during the PHD has to be performed according to clinical routine.

9.4.1 Documentation and procedures at pre-hospital discharge

- Document serial number of investigational devices used (programmer, and ECG cable PK-222-L if applicable) and version of Renamic Neo software.
- Document any adverse event or device deficiency that occurred in the respective CRFs. Adhere to the reporting timelines listed in section 18.9.
- Complete the PHD/FU source data sheet and enter data in the iMedNet EDC data base in the respective CRF.

The same procedures as for implantation (section 9.3.1) shall be documented and evaluated if performed except for procedures related to PSA functionalities.

9.5 Follow-up (only patients enrolled for follow-up case)

Patients enrolled for a follow-up case require the same enrollment and baseline documentation as described in section 9.2.

Patients can be included for any IPG, ICD, CRT or ICM follow-up. It should be assured that patients have sufficient time for the informed consent process. If applicable, patients should be informed about the study upfront by mail.

9.5.1 Documentation and procedures at follow-up

- Document serial number of investigational devices used (programmer, and ECG cable PK-222-L if applicable) and version of Renamic Neo software.
- Document any adverse event or device deficiency that occurred during follow-up in the respective CRFs. Adhere to the reporting timelines listed in section 18.9.
- Complete the PHD/FU source data sheet and enter data in the iMedNet EDC data base in the respective CRF.
- The following procedures shall be performed in the study. Perform according to clinical routine, document and assess functionalities used with the implanted device. These include for all CRM devices if applicable for the device type:
  - Sensing, pacing threshold and impedance tests
  - LV VectorOpt (only for QP leads)
  - Documentation of PNS test if performed
- Evaluate if device interrogation (including RF telemetry) and adequate programming was successful
- Assess programmable parameters (e.g. programmer preferences and PSA)
- Export programmer data files for evaluation at sponsor
- Transmit clinical documentation with the programmer for own usage and assess (data export and / or printing)
- Mobile usage of programmer with battery

9.6 Termination and post treatment

The study termination CRF must be completed to determine the date and reason for study termination of the individual patient. The regular termination of the patient is defined as the date of the pre-hospital discharge after device implantation for those patients who were included for implantation use cases. Patients who were enrolled for follow-up use cases will be terminated directly after the completion of the follow-up.

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

9.7 Description of those activities performed by sponsor representative

Qualified sponsor representatives might support the investigator during implantation or follow-up procedures as part of their general technical assistance service if this is part of the clinical routine. The interrogation and programming of the implant lies within the responsibilities of the investigator or authorized study team members who shall decide on programming parameter settings and shall conduct the assessment of safety, usability and performance of the investigational devices.

9.8 Responsibilities

9.8.1 Responsibilities of the sponsor

The sponsor of the BIO|CONCEPT.Renamic Neo is:

BIOTRONIK Australia Pty. Ltd.
Level 4, Building 2
20 Bridge St
Pymble NSW 2073
Australia

Comprehensive responsibilities regarding study conduct and management are delegated to:

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

The sponsor 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. Additionally, a summary presented in terms that are easily understandable will be made available to the intended user. According to current standard operative procedures, the CIR is written by scientist of the team Scientific Affairs based on the Clinical Investigation Plan including all amendments, the latest version of the Statistical Analysis Plan and the Statistical Analysis Report provided by the biostatistician. The CIR undergoes an internal review by the project manager, the biostatistician, and other relevant functions using a pre-specified checklist. The CIR is signed-off by the CIR writer, the project manager, the biostatistician, the Director Clinical Project Management and the representative of the local sponsor.

9.8.1.1 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).

9.8.1.2 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.

9.8.1.3 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.

9.8.1.4 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.

9.8.2 Responsibilities of the investigators

9.8.2.1 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.
- 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.

9.9 Possible influencing factors on outcome or interpretation of results

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

10 MONITORING PLAN

The responsibility of BIOTRONIK as sponsor is to ensure protocol and regulatory compliance through proper monitoring of the study. BIOTRONIK is required to ensure that the Renamic Neo programmer, software NEO 2001.A and ECG cable PK-222-L are 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, clinical investigation plan, applicable laws, 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, 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, including storage and maintenance of investigational inventory
3. Adherence to the clinical investigation plan
4. Adherence to current version of ISO 14155 and applicable local regulations and laws

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

11 STATISTICAL CONSIDERATIONS

11.1 Statistical design, method and analytical procedures

For continuous variables descriptive statistics (mean, standard deviation, median, quartiles, minimum, and maximum) will be calculated. For nominal and ordinal variables absolute and relative frequencies will be calculated based on non-missing data. Ordinal variables are described similar as continuous data (minimum, median, quartiles, and maximum) or by absolute and relative frequencies based on non-missing data of each category. Further details will be provided in the separate Statistical Analysis Plan (SAP).

11.2 Sample size

No hypotheses can be pre-specified for this clinical investigation, which is completely exploratory.

This clinical investigation should be able to identify unforeseen safety problems. While it is unlikely that the number of ADEs or DDs will be sufficient for inferential statistical conclusions, a discussion of the types of events and of the circumstances of their appearance might reveal indicators for hidden risks and trigger further dedicated investigations or statistical tests to substantiate such findings.

Unforeseen safety problems are more likely related to software problems between Renamic Neo and implanted devices but less likely to hardware problems of the Renamic Neo. Thus, the sample size is related to use cases per implantation, pre-hospital discharge, and follow-up but not to the total number of Renamic Neo devices.

11.2.1 Implantation

With reference to a statistical approach for such situations recommended by Viechtbauer et al. [Viechtbauer W et al. J Clin Epidemiol. 2015; 68:1375-9], a sample size of 50 documented implantations using a Renamic Neo would allow identifying at least one/two/three ADEs or DDs with 92 % / 72 % / 46 % confidence if any problem related to the Renamic Neo exists with 5 % probability in the population.

11.2.2 Pre-hospital discharge and follow-up

Because of the short study duration, no patient is expected to provide data from implantation or pre-hospital discharge on the one hand and follow-up on the other hand. Thus, all data are from other patients, i.e. independent samples when there is no effect of a specific Renamic Neo device effect as discussed before.

Unforeseen problems that require implant programming adjustments will be more relevant during follow-up visits. Thus 100 such use cases will be investigated. Thereby, at least one/two/three ADEs or DDs would be identified with 99%/96%/88% confidence if any problem related to the Renamic Neo exists with 5% probability in the population.

11.3 Level of significance and the power of the study

Because there are no pre-specified hypotheses, all analyses will be exploratory. For inferential analyses, a two-sided p-value less than 5% will be considered statistically significant. In accordance to the exploratory approach there will be no adjustment for multiplicity.

11.4 Expected drop-out rate

Patients that drop-out prior to any use of the Renamic Neo system investigation, e.g. withdrawal just after enrollment, will be replaced. Based on this definition, no drop-outs are expected.

11.5 Pass/fail criteria

There are no pass/fail criteria. Any potential ADEs or DDs will be analyzed and discussed.

11.6 Provision for an interim analysis

There is one planned interim analyses for internal purposes. Except for safety reasons no investigator is informed about the results and, thus, no bias is expected. There will be no adjustment for multiplicity.

11.7 Termination criteria

There is no termination of the clinical investigation on statistical grounds.

11.8 Procedures for reporting of deviations to the statistical plan

A separate SAP will be finalized after go-life of the Clinical Data Management System (CDMS) and can be updated before CDMS freeze or closure. Any deviation from the valid version of the SAP will be indicated in the Statistical Analysis Report (SAR) and clinical investigation report (CIR).

11.9 Specification of subgroups

Potential critical events will be analyzed whether there is any connection to the subgroups IPG, ICD, CRT, or ICM.

11.10 Procedure for accounting of all data for analysis

All data are entered in a CDMS by the investigators via an electronic data capture system (iMedNet, MedNet Solutions). Exports from the database will be analyzed with common validated statistical software packages (e.g. SAS 9.4 or updates, SAS Institute GmbH).

11.11 Handling of missing, unused and spurious data

For the endpoints, missing data will not be imputed. Free text will be used to clarify other data. Spurious data will be clarified via the query management system, i.e. corrected after approval of an investigator. Remaining outliers will be identified during the review of the data before CDMS closure. In case of a clear evidence of a measurement error, the Statistical Analysis Plan will be updated in order to avoid any bias. Spurious data, which were not clarified by the query process before CDMS freeze or closure, will be indicated. If appropriate, analyses will be performed both with/without such data.

11.12 Exclusion of data from confirmatory data analysis

No data are documented or analyzed from patients without documented informed consent.

11.13 Minimum and maximum number of patients per site

In order to preserve the multicentric character of the study, the number of implantations and FUs per investigational site should not exceed 30 use cases.

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.Renamic Neo 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 (FDA 21 CFR Part 11, HIPAA and EU GDPR).

Use of the clinical data management system (CDMS) will allow 24 hours 7 days a week access to the module. The PI as well as those co-investigators to whom the PI delegates data entry and authorization of CRFs need to be trained on iMedNet. After appropriate documentation of the training, user access is granted. Site staff with user access will be directed to a page where they will enter their assigned user ID and password in order to access the system. Once these have been validated, there will be options for entering a new patient or new patient data into the system.

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

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.

All principal investigators have to acknowledge the receipt of an amendment either by 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 and – if applicable – by the competent authority. 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.

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

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

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

14.4 Actions

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

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

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

Disqualification of study personnel or investigational sites is the ultimate escalation step of preventive actions. This means that in case of major deviations that seriously affect the safety and well-being of subjects or that bear a high risk of refusal of the clinical data and mistrust to the results of the study and that are likely to reappear despite other actions, the responsible person or investigational site is excluded from further conduct of the study, unless this action would jeopardize the rights, safety or welfare of the patients.

15 DEVICE ACCOUNTABILITY

The investigational devices in this clinical study are not approved for an overall market release (Renamic Neo, programmer software NEO 2001.A and ECG cable PK-222-L) and are labeled 'exclusively for clinical investigation' (Renamic Neo and ECG cable PK-222-L). They have to be stored under special conditions.

The sponsor keeps records to document the physical location of all investigational devices including the shipment of investigational devices to the investigational sites or to the local units, storage, usage and return. An electronic device accountability log is used for the documentation of the whole process. See also information on device traceability in section 4.4.

Access to investigational devices is controlled and the devices are used in the clinical investigation only and according to the CIP. The Renamic Neo will be protected by a password known only to study team members to avoid usage outside the clinical study.

The principal investigator or an authorized designee shall keep records documenting the receipt, location and return of the investigational devices. The electronic device accountability log is used for this site specific documentation. Usage will be documented in the respective CRF.

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

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

16 STATEMENT OF COMPLIANCE

16.1 Applicable ethical standards

The study will be conducted in compliance with the principles that have their origin in the Declaration of Helsinki (current version). Each step in the clinical investigation, from the initial consideration of the need and justification for the study to the publication of the results, if any, will be carried out in accordance with recognized ethical principles.

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

16.2 Applicable international and national standards

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

In deviation to ISO 14155 no coordinating investigator has been nominated for this multicenter study, as only documentation of safety, performance and usability of routine programmer usage occurs during the patient's study participation which does not require additional coordination between the PIs.

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 $\geq$ 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.

Patients, especially those included only for follow-up, should have sufficient time to be informed and decide about study participation. If applicable, patients should receive the patient information about the study upfront by mail.

17.2 Special circumstances for informed consent

Not applicable.

18 ADVERSE EVENTS AND DEVICE DEFICIENCIES

In the course of the clinical investigation, undesired medical events can occur in participating patients, users and other persons, 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 14155:2011 events will be classified on the basis of the definitions below.

18.1 Definition of adverse events

An AE is defined* as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons whether or not related to the investigational device. This includes:

- Events related to the investigational device
- Events related to the procedures involved
- For users or other persons, this definition is restricted to events related to the investigational devices.

*see ISO 14155 3.2

18.2 Definition of adverse device effects

An adverse device effect (ADE)* is an AE that is related to the use of an investigational device. This includes any AE resulting from insufficient or inadequate instructions for use or the deployment, implantation, installation, or operation, or any malfunctioning of the investigational device and any event resulting from use error or from unintentional misuse of the investigational device.

*see ISO 14155 3.1

18.2.1 Causality Assessment

The relationship between the use of the investigational device (including the medical-surgical procedure) and the occurrence of each adverse event shall be assessed and categorized, considering the presence of confounding factors, such as concomitant medication and treatment, the natural history of the underlying disease, other concurrent illness or risk factors.

Each AE will be classified according to five different levels of causality. As defined in the Meddev 2.7/3 rev 3, the investigator will use the following definitions to assess the relationship of the adverse event to the investigational device or procedures and the sponsor will review the investigators categorization:

Not related: the relationship to the device or procedures can be excluded

Unlikely: the relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.

Possible: the relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness / clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.

Probable: the relationship with the use of the investigational device seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained.

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

The investigators will distinguish between the adverse events related to the investigational device and those related to the device procedures (any procedure specific to the investigational device). Procedure related events refers to the procedure related to the application of the investigational device only and therefore not to any other procedure for other devices and not to any other procedures or treatments applied later throughout the clinical investigation, for instance to treat (serious) adverse events. In case of a replacement of the investigational device in response to an adverse event (e.g. programmer replacement after failed implant interrogation), the replacement will be considered like an initial application of a new investigational device and shall be assessed accordingly.

AEs that occur during implantation are not considered as ADEs related to the investigational device procedure unless the implementation/use of the investigational device, in this case the programmer, caused the AE. For example, the RF telemetry failed and the implant device could not be programmed appropriately which caused an AE.

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

18.3 Definition of device deficiency

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

*see ISO 14155 3.15

DDs of the investigational device shall be documented throughout the study. DDs which caused an adverse event are reported on the respective adverse event form. In case the DD did not cause an adverse event the provided DD form shall be used to document this 'non-medical' event.

If a DD could have led to a SADE,

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

the DD is classified as an DD with an SADE potential.

18.4 Definition of serious adverse events

AEs are classified as serious* if one or more of the following consequences are fulfilled:

- led to death
- led to serious deterioration in the health of the subject, that either resulted in
  - a life-threatening illness or injury, or
  - a permanent impairment of a body structure or a body function, or
  - in-patient or prolonged hospitalization, or
  - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
- led to fetal distress, fetal death or a congenital abnormality or birth defect.

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

*see ISO 14155 3.37

In-patient hospitalization is defined as at least one overnight stay (change of date) in a hospital. In case, a patient is only for some hours in the hospital (without change of date), this event will not be documented as serious, unless one or more of the other seriousness criteria are fulfilled.

18.4.1 Patient death

If the death of a patient emerges during the study this SAE might be subject to special reporting requirements in some countries. Therefore as much information as possible should be provided to enable BIOTRONIK to explain the circumstances leading to the death. At least a 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 shall be sent to BIOTRONIK promptly.

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

- Cause of death
- Date and time of death
- Place death occurred
- Statement whether the event was device or study procedure related

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

18.5 Definition of serious adverse device effect

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

*see ISO 14155 3.36

18.6 Definition of unanticipated serious adverse device effects

SADEs* are defined as unanticipated if by their nature, incidence, severity or outcome they have not been identified in the current version of the risk analysis report.

*see ISO 14155 3.42

These events must be reported to the sponsor immediately.

A root-cause analysis will be performed and the possibility of reoccurrence will be evaluated immediately.

Note: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

18.7 Anticipated adverse events

As the Renamic Neo systems is not yet approved, only clinical data of it is predecessors including Renamic or programmers in general are available.

The available data does not allow a precise calculation of complication rates (e.g. per application or per patient-year). Nevertheless, considering the number of sold devices (e.g. more than 20,000 Renamic programmers worldwide) and their frequent use, the data suggest that clinical complications associated with the devices are rather rare. However, due to the nature of their application and the associated risk, adverse events, including serious adverse events, cannot be ruled out.

A summary of the clinical complications reported in the MAUDE database and in BIOTRONIK sources is provided. The following sources were searched for relevant information on adverse events and adverse device effects related to the investigational devices:

- Systematic literature search using programmer related terms
- Manufacturer and User Facility Device Experience Database (MAUDE)
- BIOTRONIK vigilance database

A systematic literature search using programmer related search terms was performed. The search did not retrieve any relevant hits (Table 4). This low yield is in line with previous systematic searches for programmer devices.

Table 4: Literature search results for CRM device programmers.

Search term	Initial results	After title screening	After abstract screening	After full text screening (Selected publications)
(programmer OR "pacing system analyzer" OR "pacing system analyser" OR PSA) AND (pacemaker OR defibril* OR IPG OR ICD OR bradycardia OR tachycardia OR loop recorder OR ICM OR ILP) AND ("complication"[Title/Abstract] OR "complications"[Title/Abstract] OR "adverse event"[Title/Abstract] OR "adverse events"[Title/Abstract] OR safety[Title/Abstract]) AND ("2009/01/01"[PDAT] : "2019/12/31"[PDAT]) AND "humans"[MeSH Terms]	18	12	0	0

Source: PubMed

Therefore, a comprehensive overview of clinical complications for this device group cannot be generated based on scientific literature.

The FDA Manufacturer and User Facility Device Experience Database (MAUDE) was examined to understand the number and types of adverse events for currently approved CRM programming devices.

MAUDE data represents reports of adverse events involving medical devices. MAUDE data is not intended to be used either to evaluate rates of adverse events or to compare adverse event occurrence rates across devices. Submission of the report does not mean the device caused the adverse event. In most cases, further investigation is necessary to understand the cause of the adverse event.

Table 5: Overview of adverse events reported in the MAUDE database

Adverse event term	**Programmer**					
	BIOTRONIK	Medtronic	Boston Scientific	Abbott	MicroPort	Vitatron
Death	0	2	0	1	0	0
Asystole	1	0	0	5	0	0
Syncope	0	0	0	2	0	0
Inappropriate shock	0	0	0	1	0	0
Electrical shock	2	0	0	24	0	0
Pain	0	1	0	0	0	0

The three death cases described in **Table 5** occurred during programmer use but according to the case descriptions it is unlikely that they are related to the programmer.

More than 300.000 implantations of IPGs or ICDs are performed in the US per year and several million patients are interrogated during follow-ups with a programming device [14–18]. Considering these high numbers of applications of the programmer the number of reports of adverse events in the MAUDE data base is low.

Data from the vigilance database of BIOTRONIK's Center for Clinical Research (CCR) were analyzed to identify adverse events or device deficiencies that are possibly related to the following programming devices and their accessories[19]:

- Renamic
- Renamic PSA
- ICS 3000
- PSW (software)
- PK-222
- other accessories (e.g. PGH, pen, USB)

The analysis covered data from ~8,800 study patients collected from 2014 to 2019. The data origins from studies with ICMs, IPGs, ICDs, and CRT-devices.

Fourteen AEs were identified, in which the case description contained one or more of the search terms in one or more of the four text fields. None of the events was related to a BIOTRONIK product [19,20]

Depending on the patient's condition and depending on the scope and type of pacing program, the following possible complications associated with the use of pacing system analyzers are reported in medical references: life-threatening atrial and ventricular arrhythmia, bradycardia, tachycardia, and asystole.

18.8 Reporting responsibilities

18.8.1 Reporting responsibilities of the investigator to sponsor

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

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

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

The reports shall be done with all information available, even if this results in an incomplete report. The investigator has to follow-up ongoing (S)A(D)Es either as long as the patient participates in the study, the clinical investigation is terminated prematurely or until the event has been resolved, whatever comes first. Ongoing SADEs related to the investigational device will be followed for a maximum time period of either 2 weeks after pre-mature or regular study termination of the individual patient.

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. 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.

18.8.2 Reporting responsibilities of the investigator to other parties

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

18.8.3 Reporting responsibilities of the sponsor

BIOTRONIK SE & Co. KG will report all serious adverse events (SAEs)/serious adverse device effects (SADE) and all device deficiencies with a SADE potential to the competent authority depending on the local regulatory requirements.

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

BIOTRONIK SE & Co. KG will inform the investigators about all reported SAEs and DDs that could have led to 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.

18.9 Reporting timelines

The reporting timelines for the investigator are displayed in Table 6.

Table 6: 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 24h after detection

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

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

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

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

18.10 Emergency contact

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

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

18.11 Data (safety) monitoring committee

Not applicable.

19 VULNERABLE POPULATION

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

20.2 Un-blinding procedures

Not applicable.

20.3 Requirements for subject follow-up

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

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

If an (S)A(D)E is ongoing at time of the last study related visit or study termination, whatever comes first, the outcome of the event has to be updated to 'Ongoing at study termination'. Ongoing SADEs related to the investigational device will be followed for a maximum time period of either 2 weeks after pre-mature or regular study termination of the individual patient.

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

21 PUBLICATION POLICY

21.1 Decision for publication

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

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 an abstract to a congress within one year after finalization of the clinical investigational report. Moreover, the results of the study will be published in the publicly accessible database (see above). Due to the limited amount of clinical data collected within this study, a manuscript publication seems not feasible.

The abstracts will be reviewed and approved by all authors and BIOTRONIK.

21.2 Authorship guidelines

Purpose of this authorship guideline is to settle criteria which of the contributors to this study should be identified as authors. It is valid for all contributors to the study, including investigators, sponsor employees, and other individuals contracted by the sponsor.

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

1) Substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data,
2) drafting the article or revising it critically for important intellectual content, and
3) final approval of the version to be published.

For the planned congress contribution, acquisition of data will be weighted based on the number of reported use cases. First authorship will be offered to the principal investigator that included the highest number of use cases.

The first author takes the responsibility for the following actions:

- Guarantee the integrity of the publication
- Support members of BIOTRONIK in preparation of abstract, poster, presentation – especially regarding the medical perspective
- Presentation at the congress or delegation of a substitute
- Disclose potential conflicts of interest

All co-authors have the following tasks and responsibilities:

- Review of abstract, poster, presentation and give feedback within the determined time window
- Agree on the order in which they appear in the publication
- Agree on any changes in authorship
- Disclose potential conflicts of interest

No honoraria will be paid for authorship of publications.

21.3 Contributorship and acknowledgement

Individuals, including BIOTRONIK employees, who have substantially contributed to a study, but who do not meet the authorship criteria, should be listed in the acknowledgement section. Any support provided by a professional medical writer must also be disclosed in the acknowledgement section.

21.4 Ancillary publications

There are no ancillary manuscript publications planned.

22 BIBLIOGRAPHY

Literature Cited

1. Morschhäuser D, Fischer W, Jakob M. *Praxis der Herzschrittmacher-Nachsorge: Grundlagen, Funktionen, Kontrolle, Optimierung, Troubleshooting* (3rd edition). Berlin: Springer Berlin; Springer, 2019.
2. Ellenbogen KA, Wilkoff BL, Kay GN, Lau C-P, Auricchio A, editors. *Clinical cardiac pacing, defibrillation, and resynchronization therapy*. Philadelphia, PA: Elsevier, 2017.
3. Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt O-A *et al.* 2013 ESC guidelines on cardiac pacing and cardiac resynchronization therapy: The task force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). *Europace* 2013;**15**:1070–1118.
4. BIOTRONIK SE & Co. KG. *Technical Manual - Renamic Neo: Medical Programmer and Monitoring Device*., 2019.
5. BIOTRONIK SE & Co. KG. *Technical Manual - Programmer SW PSW NEO: Software PSW NEO version 2001.A for the following BIOTRONIK programmer: Renamic Neo*., 2019.
6. BIOTRONIK SE & Co. KG. *Technical Manual - PK-222, PK-222-L, PK Electrode Clip: Patient cable for programmers*., 2019.
7. BIOTRONIK SE & Co. KG. *Investigator's Brochure for the BIO|CONCEPT.Renamic Neo Study*., 2019.
8. BIOTRONIK SE & Co. KG. *QP ExCELs Study, Clinical Investigation Report*., 2017.
9. BIOTRONIK SE & Co. KG. *Eluna Family / Sentus BP Master Study, Clinical Investigation Report*., 2016.
10. BIOTRONIK SE & Co. KG. *MATRIX, Clinical Investigation Report*., 2019.
11. BIOTRONIK SE & Co. KG. *BIO|MASTER.Ilivia Family / Plexa, Final Clinical Investigation Report*., 2018.
12. BIOTRONIK SE & Co. KG. *BIO|MASTER.BioMonitor 2, Clinical Investigation Report*., 2017.
13. BIOTRONIK SE & Co. KG. *Functional System Risk Analysis - Programming Device for Implantable Pacemakers, Defibrillators and Monitors incl. Programmer Software (General) (FSR-111-002)*., 2019.
14. Mond HG, Proclemer A. The 11th world survey of cardiac pacing and implantable cardioverter-defibrillators: Calendar year 2009--a World Society of Arrhythmia's project. *Pacing Clin Electrophysiol* 2011;**34**:1013–1027.
15. Greenspon AJ, Patel JD, Lau E, Ochoa JA, Frisch DR, Ho RT *et al.* Trends in permanent pacemaker implantation in the United States from 1993 to 2009: Increasing complexity of patients and procedures. *J Am Coll Cardiol* 2012;**60**:1540–1545.
16. Ogunbayo GO, Charnigo R, Darrat Y, Morales G, Kotter J, Olorunfemi O *et al.* Incidence, predictors, and outcomes associated with pneumothorax during cardiac electronic device implantation: A 16-year review in over 3.7 million patients. *Heart Rhythm* 2017;**14**:1764–1770.
17. Friedman DJ, Parzynski CS, Varosy PD, Prutkin JM, Patton KK, Mithani A *et al.* Trends and In-Hospital Outcomes Associated With Adoption of the Subcutaneous Implantable Cardioverter Defibrillator in the United States. *JAMA Cardiol* 2016;**1**:900–911.
18. Buckley U, Shivkumar K. Implantable cardioverter defibrillators: Even better than we thought? *Eur Heart J* 2015;**36**:1646–1648.
19. BIOTRONIK SE & Co. KG, J. Schrader. *Analysis Report - Adverse Events (AEs) or Device Deficiencies (DD) possibly related to the programming device and accessories*., 2019.
20. BIOTRONIK SE & Co. KG. *Post Market Surveillance Report (Renamic, pace sense analyser module (PSA) and ECG-Cable PK-222)*., 2019.