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10 RESPONSIBILITIES

10.1 Responsibilities of the sponsor

The sponsor of the BIO|CONCEPT.Amvia 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 and the Center for Clinical Research ensure that all documents, information and necessary human resources are made available for initiation, conduct and termination of the study.

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

- Maintaining insurance cover or indemnification of patients in case of injury in accordance with applicable laws.
- Contracting of investigational sites and investigators.
- Responsibility for all payments and financial coverage of the study.
- Selection of suitable investigational sites, investigators and clinical monitors.
- Creating a Master template for informed consent form and obtain approval of the Master template by the leading ethics committee (EC), if required.
- Obtaining of a favorable ethics vote(s) for conduct of the clinical study.
- Obtaining approval of the involved competent authorities (if applicable).
- Training of all investigators by BIOTRONIK personnel on the use of the Amvia Sky pacemakers, the programmer software and the HMSC prior to study start.
- Supervision of study conduct according to the legal regulatory requirements and the requirements of the CIP.
- Fulfill reporting duties of the sponsor to the ethics committees and regulatory authorities.
- Data analysis and data management.
- Performance of on-site audits as planned routine audits, on demand in case of detected non-compliances, or as preparation for an announced inspection by a Competent Authority.
- Provision of the final clinical investigation report (CIR) in accordance with applicable legal requirements and ethical principles.

10.1.1 Project management

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

- Development of the clinical investigation plan and possible amendments.
- Coordination of all study-related activities dedicated to the sponsor.
- Support of investigational sites during the study (obtaining ethics committee votes, etc.).
- Continuous information of investigational sites and clinical monitors on study progress.

- The clinical project manager is supported by other staff members of the sponsor (e.g. in-house clinical research associates, data assistants, database managers).

10.1.2 Data management

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

- Development and maintenance of the clinical data management system (CDMS; iMedNet of the company MedNet Solutions Inc, Minnetonka, MN 55305 USA).
- Development of the data management plan.
- Development of the CRF user guide.
- Data management.

10.1.3 Biostatistician

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

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

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

10.1.4 Monitor

The sponsor names clinical monitors for each participating investigational site prior to initiation of the respective site. Names and contact data will be provided to the investigational sites in due time. In case of changes, the investigational site will be informed by the sponsor. An adequate monitoring will be ensured by the sponsor. Monitoring will be conducted according to the SOPs of the sponsor. Responsibilities of the clinical monitors are described in section 11 of this document.

10.2 Responsibilities of the investigators

10.2.1 Coordinating investigator

The clinical study BIO|CONCEPT.Amvia is coordinated by:

The responsibilities of the CI are listed in the following:

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

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

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

10.2.2 Investigator

The study shall be conducted by qualified investigators.

- Implantations shall be performed by an interventional cardiologist with at least 3 years experience with pacemaker implantations.

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.
- Obtaining of a positive vote of the ethics committee responsible for the investigational site.
- Safeguarding the rights and the physical and mental integrity as well as the privacy and the protection of the data of the study patients.
- Adverse Event reporting according to the clinical investigation plan.
- Recruitment of suitable patients in an adequate time frame.
- Patient information and obtaining of written informed consent of the patient according to the requirements of the CIP.
- Safe and efficient use of devices.
- Inform the sponsor about new study team members before authorizing them for study related activities.
- Provide the sponsor with required documentation for assessing the qualification of study team members.
- Authorize co-investigators only after documented adequate study specific training.
- Discourage patients to consent for other interventional clinical investigations, in case the investigator is aware of such intentions beforehand. Inform the sponsor, in case a patient has already been enrolled into another interventional clinical investigation without undue delay. Obtain the sponsors permission before enrolling the patient into another interventional clinical investigation.
- Conduct of the study according to the CIP
- Provide the sponsor with an ISO 14155 or GCP training certificate
- Data collection and data entry in accordance with the requirements of the CIP. Patient records shall include the relevant medical history and progress of the disease of each patient.
- Providing supporting material, if necessary.
- Submission of safety reports and protocol deviations to ethics committee and competent authorities (if applicable).
- Support of monitoring and auditing activities.
- Confidential treatment of all study-related documents and information.

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

11 MONITORING PLAN

The responsibility of BIOTRONIK as sponsor is to ensure protocol and regulatory compliance through proper monitoring of the study. BIOTRONIK is required to ensure that the investigational devices 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, the clinical investigation plan, applicable laws, and 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, or by authorized BIOTRONIK designees) to ensure that the investigator and the clinical investigation team conducts the clinical investigation in accordance with the CIP, The Declaration of Helsinki, ISO 14155, and applicable laws and regulations to ensure adequate protection of the rights, safety and wellbeing of patients and the quality and integrity of the resulting data. Remote source data verification may be performed in case of pandemic situations if remote access to the site's patient files can be granted to the monitor.

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. The monitoring plan may also include provisions for remote monitoring measures in case that site access is restricted, e.g. due to a pandemic situation.

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 21).

12 STATISTICAL DESIGN AND ANALYSIS

No hypotheses were formulated, and no endpoints defined for this study. For more information on objectives and study design, see chapters 7 and 8.

12.1 Analysis population

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

12.2 Descriptive statistics

Standard descriptive statistical methods are used depending on the type of the available data. For continuous variables, mean value, standard deviation, median, minimum, maximum and quartiles are calculated. For nominal variables, absolute and relative frequencies are calculated based on non-missing data. For ordinal variables, median, minimum, maximum and quartiles or absolute and relative frequencies are calculated for each category based on non-missing data. The SADE-free rate is calculated using the Kaplan-Meier estimate after 12 months.

12.3 Analytical procedures

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

12.4 Significance level, statistical power, and statistical testing

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

12.5 Sample size

This clinical investigation should be able to identify unforeseen safety problems. With reference to a statistical approach for such situations recommended by Viechtbauer et al.[21], a sample size of 50 documented implantations with Amvia Sky devices would allow identifying at least one/two/three ADEs or DDs with 92 % / 72 % / 46 % confidence if any problem related to the devices exists with 5 % probability in the population.

12.5.1 Expected outcome(s)

Not applicable.

12.5.2 Adjustments due to interim analyses

Not applicable.

12.5.3 Detectable effect size and non-inferiority margin

Not applicable.

12.5.4 Randomization allocation ratio

Not applicable.

12.5.5 Expected drop-out rate

Patients that drop out prior to any implantation attempt, or patients who are not implanted with an investigational device and who did not come into contact with any investigational device during implantation attempt can be replaced. However, we expect a drop-out rate of 5-10% during the follow-up phase.

12.6 Number of Procedures

There is no requirement for a minimum number of procedures to be performed by a specific investigator and no pre-planned analysis of such data.

12.7 Pass/fail criteria

Not applicable.

12.8 Interim analyses

It is planned to perform an interim analysis for the internal evaluation of product performance and for the validation of promotional claims at the end of the enrollment period. Additionally, specific data might be provided to competent authorities, if requested.

12.9 Bias

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

See also chapter 8.1.2.

12.10 Confounding factors

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

12.11 Multiplicity

There is no multiplicity control foreseen.

12.12 Subgroups

If required, SR-T, DR-T, HF-T QP devices as well as men and women can be analyzed separately. The safety analysis will be provided for the total study population.

12.13 Missing, unused, and spurious data

All data needed to be analyzed are pre-documented in a Statistical Analysis Plan (SAP). Other data from the Clinical Data Management System (CDMS) might be needed for case reports, e.g. in case of Adverse Events.

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

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

12.14 Exploratory analysis and sensitivity analysis

Because there are no pre-specified hypotheses, all analyses are exploratory and there is also no specific sensitivity analysis.

12.15 Deviations from the original statistical plan

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

12.16 Imbalance in multicentre clinical investigations

is divided into two approximately equal groups with higher and lower enrollment to compare the SADE-free rates between the two groups.

12.17 Data pooling

Not applicable.

13 DATA MANAGEMENT

13.1 Methods for data entry and collection

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

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

Investigational medical device data will be collected as outlined in the CIP and consented to by the patient in the ICF. The collected device data is transferred securely and automatically to the Home Monitoring Service Center (HMSC) of BIOTRONIK. Following this transfer to the HMSC, device data will be securely transferred in an approved and validated manner to the Clinical Data Warehouse (CDW) at BIOTRONIK, where it can be used for analysis according to the CIP. Only trained and approved study personel of BIOTRONIK can access the investigational device data in the CDW.

Every access and every change to the medical and device data of the clinical investigation is recorded by an independent audit trail in the CDMS and CDW.

For the majority of the CRF entries source data needs to be maintained at the site and will be collected in adequate files (e.g. patient files). The data has to be stored and shall be made available upon request in order to allow source data verification. Exceptions for which the CRF entry can be regarded as source data are indicated in the monitoring plan or at the respective section of the CIP.

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

Specific, timely, and reliable processes for recording data and rectifying errors and omissions, medical coding uniformity, and reconciliation, if applicable, are necessary to ensure delivery of a quality database and to achieve the clinical investigation objectives. The study specific quality control measures are applied at every stage of data handling and described in detail in the clinical data management plan and monitoring plan.

During the data entry and query management with the CDMS, the status of medical centers, patients, CRF and queries are tracked and displayed with the CDMS. In addition, a defined workflow with colored icons, lists, and tasks is also provided in the CDMS to ensure that queries are resolved in a timely manner. The lists and tasks are presented according to the role in the study team and medical centers. Furthermore, notifications of the current CRF status can be sent to defined recipients by email.

The CRFs will be checked against source data by clinical monitors as described in the monitoring plan. Errors, discrepancies, missing data, and entries out of range are resolved both automatically (CDMS) and manually (clinical monitor, clinical data manager) via queries and deviation forms.

The investigational site is obliged to answer all incoming data queries and deviation forms in due time to clarify the open issues. Corrections to the CRF can only be done by the designated site personnel and have to be signed by an authorized investigator thereby approving the completeness and correctness of the data.

Additionally, after data entry into the CDMS, the clinical data is automatically checked with programmed quality checks within CDMS.

The CDMS supports detailed tracking of the query process since all changes are automatically recorded in the system audit trail.

Additional quality control measures of clinical data include:

1. performing quality control on whole study populations, especially for variables that are related to endpoint evaluations, identify data processing errors, correction of such errors, communication and feedback of study team and medical staff during and after completion of a study;
2. identifying and documenting protocol violations with the CDMS, missing or unprocessed documents, early terminations, and any other special situations regarding patients that may influence the data analysis; reporting any special data processing situations or deviations from defined conventions (e.g. coding of Adverse Event);
3. comparing trial data at multiple timepoints;
4. monitoring data at the site to detect which data differs significantly between source and CRF, so that appropriate corrective actions can be taken;
5. using of statistically quantitative reports to measure data quality and
6. identifying and providing feedback concerning problems with the study specific CDMS.

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

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

An authenticated user account is created and maintained by BIOTRONIK for each authorized user once the user has completed the appropriate training. Users are obligated to keep their password confidential.

Depending on their role within the investigational study, users are limited to ‘read only’ or may be given permits to enter or update data, provide resolutions to queries and apply electronic signatures. Only investigators are allowed to sign the entries. The user role and rights management is documented accordingly.

13.4 Procedures to maintain and protect subject privacy

The general data protection regulation GDPR (EU) 2016/679 and related EU contractual clauses are implemented by the service provider MedNet Solutions, Inc., for CDMS and BIOTRONIK.

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

All patient-related data and information received from the clinical study will be handled confidentially and pseudonymized. The collected data will be securely transmitted to BIOTRONIK for electronic data processing, safety reporting and analysis in compliance with the data

protection law. The data will be pseudonymized at the sites before transmission, without using patient initials. To ensure traceability of patient data, but preventing unauthorized identification of individual patients, a pseudonymized patient ID is used that consists of a clinic number and a consecutive number for the patient, however no additional patient identification characteristics. All clinical data will be stored in the validated electronic system environment with adequate and documented protection against unauthorized user access. Access will be given to responsible EC and CA upon approved 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 study in the patient informed consent form. Specifically, all patients will be educated about their rights concerning data access, data correction, and data deletion according to applicable legislation.

The patient identification log sheet, in which the patient ID code, name, date of birth and date of informed consent is entered, will remain at the investigational sites. No copies of the patient identification log sheet will be provided for the sponsor. The patients will be informed on the fact that exact identification of the patient is only possible for the investigator.

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

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

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

- all expected data retrieved,
- all received data cleaned (i.e. all discrepancies have been raised and resolved for all expected data),
- all electronic data received, loaded, reconciled and cleaned,
- all coding completed and
- SAE and AE reconciliation completed.
- for final data analysis, all relevant data are checked by the biostatistician.

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

13.6 Procedures for data retention

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

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

All study related data and electronic documents are stored in the archive of BIOTRONIK which provides storage conditions free from risk of fire, flood, theft and vermin. The access to the files is controlled.

All relevant study related documents have to be stored in the Investigator Site File at the investigational sites. Documents containing patient's data, raw data and other study related documents have to be archived in the investigational site. In case of electronic source data (e.g. electronic patient files) adequate actions have to be taken to ensure data availability during the complete archiving period.

13.7 Specified retention period

Investigational data are stored electronically for at least 15 years after last patient out on the archive server. At the end of this period, requirements from laws and other regulations will be reconsidered in order to decide whether the retention period must be extended or data must be deleted.

14 AMENDMENT PROCEDURES

If throughout the course of the study changes to the clinical investigation plan (CIP) are deemed to be necessary, a change justification has to be prepared which includes the rationale and content of the adjustment. The modification of the CIP can either be summarized in a separate document as an attachment to the current applicable version of the CIP or result in a new version of the CIP.

If the changes have impact on study related procedures or data analysis they are substantial by definition.

New versions of the CIP or substantial amendments have to be reviewed and confirmed by the coordinating investigator. All principal investigators have to acknowledge the receipt of an amendment by either signing the CIP acknowledgement page which is part of the CIP, or by signing the amendment agreement form if no new CIP version was created.

Before implementation of any changes, substantial amendments have to be approved by the Ethics Committee (EC) and – if applicable – by the Competent Authority (CA). Non substantial amendments are submitted for notification only.

The investigator should not implement any deviation from or changes to the CIP without agreement of the sponsor and prior review and documented approval from the EC (and CA if required). The only exception is the necessity to eliminate an immediate hazard to the patients, or when the change involves only logistical or administrative aspects of the study.

15 DEVIATIONS FROM CLINICAL INVESTIGATION PLAN

15.1 CIP compliance and exceptions

All sponsor personnel, all investigational site personnel as well as other third parties, who are involved in tasks covered by this CIP, are generally obliged to comply with this CIP.

A deviation is any failure to follow, intentionally or unintentionally, the requirements of the CIP, including laws, guidelines and other regulation as far as required by the CIP and applicable laws, as well as applicable amendments. Deviations that are likely to seriously affect or that actually have seriously affected the rights or safety or wellbeing of patients or the scientific integrity of the clinical investigation are major deviations. Otherwise they are minor deviations.

Erroneous, spurious or missing data in a CRF is not a deviation in itself and is handled according to the query processes described in the data management section of this CIP. However, the underlying reason might be a deviation.

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

No waivers from the CIP are allowed.

15.2 Recording, reporting and analyzing deviations

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

15.2.1 Site specific deviations

Investigational sites are obliged to record any deviation immediately as they become aware of it. In addition, compliance to the CIP is verified by the sponsor through the clinical monitor. Each site specific deviation is assessed for the need of corrective or preventive actions.

15.2.2 Other deviations

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

15.2.3 Reporting

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

15.3 Notification requirements and timelines

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

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 in Australia. 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.

15.4 Actions

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

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

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

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

16 DEVICE ACCOUNTABILITY

Investigational devices which are not approved for an overall market release and are labeled 'exclusively for clinical investigation' have to be stored under special conditions.

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

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

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

The responsible clinical monitor checks the storage, usage and documentation and verifies the completeness of the device accountability log in the CDMS regularly during their visits.

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

17 STATEMENT OF COMPLIANCE

17.1 Applicable ethical standards

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

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

17.2 Applicable international and national standards

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

The study will also be conducted according to the applicable national legal requirements.

17.3 Ethics committee and competent authority

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

17.4 Adherence to additional requirements

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

17.5 Patient insurance

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

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

17.6 Financing

This clinical investigation is financed by the sponsor BIOTRONIK Australia Pty. Ltd.. Contracting of investigation sites and investigators is in the responsibility of the sponsor, as mentioned in section 9.10.1 'Responsibility of the sponsor'. The agreement between the sponsor and the research site determines inter alia the following aspects: conducting the contract research, obligations of the sponsor/the investigational site/the investigator, fee payments of the sponsor, intellectual property and publication of research results, confidentiality, insurance coverage and compliance with applicable laws/regulations and ethical standards.

18 INFORMED CONSENT PROCESS

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

18.1 General considerations

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

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

The date of the informed consent discussion as well as the date of patient's signature of the informed consent form shall be documented in patient's medical record. If the first study-specific procedure, e.g. implantation, is performed on the same day, the time of patient´s signature shall be documented on the informed consent form and in the medical record as well. A copy of the signed and dated written informed consent form is provided to the patient. Both signatures need to be obtained before any study related procedure. The investigator ensures that no patients are included in this clinical study who are unable to give informed consent by selecting patients with age ≥ 18 years, who understand the nature of the procedure.

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

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

18.2 Special circumstances for informed consent

Not applicable.

19 ADVERSE EVENTS AND DEVICE DEFICIENCIES

In the course of the clinical investigation, undesired medical events can occur in participating patients, which are called adverse events (AEs) in the following. Furthermore, device deficiencies (DD) may also be observed. All AEs and all 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.

Any person who identifies an event or relevant information that could have an impact on patients', users' or other persons' safety, has an obligation to inform the investigator and the sponsor of their concerns.

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

According to ISO 14155:2020 events will be classified on the basis of the definitions below.

19.1 Definition of adverse events

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

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

*see ISO 14155:2020 3.2

19.2 Definition of adverse device effects

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

*see ISO 14155:2020 3.1

19.2.1 Causality Assessment

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

Each AE will be classified according to four different levels of causality. As defined in the MDCG 2020-10/1 'Safety reporting in clinical investigations of medical devices under the Regulation (EU) 2017/745', the investigator will use the following definitions to assess the relationship of the adverse event to the investigational device or procedures and the sponsor will review the investigators categorization:

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

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

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

Causal relationship: Causal relationship: the 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.

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. For example, an event related to the implantation of a cardiac lead will not be considered as related to the procedure of investigational device use since the leads are not specific for the use of the Amvia Sky pacemakers.

19.3 Definition of device deficiency

Device deficiency (DD)* is defined as inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance, including malfunctions, use errors and inadequacy in the information supplied by the manufacturer including labelling. This includes DDs related to the investigational medical device or the comparator.

*see ISO 14155:2020 3.19

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

If a DD could have led to an SADE,

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

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

19.4 Definition of serious adverse events

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

- led to death
- led to serious deterioration in the health of the subject, users, or other persons as defined by one or more of the following:
  - a life-threatening illness or injury, or
  - a permanent impairment of a body structure or a body function including chronic diseases, or
  - in-patient or prolonged hospitalization, or
  - medical or surgical intervention to prevent life-threatening illness or injury, or permanent impairment to a body structure or a body function.
- led to foetal distress, foetal death, or a congenital abnormality, or birth defect including physical or mental impairment.

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

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.

*see ISO 14155:2020 3.45

19.4.1 Patient death

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

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

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

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

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

19.5 Definition of serious adverse device effect

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

*see ISO 14155:2020 3.36

19.6 Definition of unanticipated serious adverse device effects

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

*see ISO 14155:2020 3.51

These events must be reported to the sponsor immediately.

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

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

19.7 Definition of serious public health threat

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

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

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

19.8 Anticipated adverse events

Table 4 provides an overview of anticipated adverse events and their frequencies according to literature. For all references used in this table, refer to the list at the end of this section.

Table 4: Frequency of anticipated adverse events

Frequency	Event Type	Reference ID
Frequent >(10.0%)	Shoulder pain	[10]
	Device stimulation issue (LV-lead)	[5]
Probable >(1.00%); ≤(10.0%)	Device lead issue (LV-Lead)	[6, 32]
	Oversensing (Total)	[42, 47, 69]
	Device lead issue (Total)	[4, 24–31]
	Lead dislodgement (LV-Lead)	[6, 18–21]
	Device capturing issue (LV-Lead)	[46]
	Implant site reaction (Total)	[4, 7–10, 12–15, 24, 26–28, 30–41, 45, 49–65, 70–73]
	Device stimulation issue (Total)	[3–8]
	Oversensing (RV)	[42, 69]
	Lead dislodgement (RA-Lead)	[6–15, 17, 20, 22, 23]
	Device dislocation	[12, 30, 48]
	Implant site haematoma	[4, 7–10, 13–15, 24, 27, 28, 30–32, 34–37, 49, 51–53, 56–63, 65, 70–73]
	Device lead damage (RV-Lead)	[42]
	Device capturing issue (RV-Lead)	[12, 42, 43]
	Device lead issue (RA-Lead)	[23, 32–35]
	Nerve injury	[10, 49]
	Lead dislodgement (RV-Lead)	[7, 9–17]
	Haemorrhage (Total)	[7, 26, 36–41]
	Implant site haemorrhage	[7, 26, 36–41]
	Complication of device insertion (LV-Lead)	[6]
	Device capturing issue (Total)	[6, 12, 42–44, 46, 47]
	Device lead issue (RV-Lead)	[23, 32, 33, 35]
	Oversensing (RA)	[69]
	Implant site erosion	[7, 8, 10, 12, 30, 45, 54]
	Device pacing issue (RV-lead)	[14, 42, 43]
	Pain (Total)	[4, 10, 14, 28]
	Device pacing issue (Total)	[7, 8, 14, 19, 42–45]
	Incision site impaired healing	[8, 65]
	Vessel puncture site phlebitis	[10, 55]

Frequency	Event Type	Reference ID
	Device electrical impedance issue (RV-Lead)	[42]
	Implant site reaction (Total, during an MRI procedure)	[74]
	Implant site paraesthesia (during an MRI procedure)	[74]
Occasional >(0.10%); ≤(1.00%)	Implant site infection	[7, 8, 13, 14, 28, 30, 31, 33, 36, 45, 49, 50, 52–55, 59, 60, 64, 65]
	Infection (Total)	[4, 7, 8, 10, 12–15, 17, 19, 20, 24–34, 36, 37, 45, 46, 48–68]
	Medical device site discomfort	[7, 64]
	Ventricular tachycardia	[58]
	Pacemaker syndrome	[8, 33, 59]
	Device pacing issue (RA-lead)	[14]
	Ventricular arrhythmia	[30]
	Pneumothorax	[4, 6–8, 10, 13–15, 20, 22, 24, 26–28, 30–32, 35, 36, 41, 45, 49, 51, 55, 56, 58, 60–65]
	Implant site pain	[4, 10, 28]
	Undersensing (RA)	[14, 15, 69]
	Thromboembolic event	[36, 38, 60]
	Undersensing (Total)	[14, 15, 43, 69]
	Device capturing issue (RA-Lead)	[46]
	Device pacing issue (LV-lead)	[19]
	Device related infection	[12, 15, 17, 19, 20, 24, 27, 34, 37, 46, 48, 55, 56, 62–64, 66, 67]
	Device computer issue	[7]
	Endocarditis	[3, 7, 24, 25, 28, 30, 31, 33, 50, 53, 55, 64]
	Cardiac perforation/Cardiac tamponade/Pericardial effusion (Total)	[4, 7, 10, 11, 13, 15, 16, 23–29, 31, 32, 35–37, 41, 44, 49, 51, 55, 56, 58–61, 63, 64, 71, 74, 75]
	Device electrical impedance issue (Total)	[7, 42, 47]
	Pericardial effusion	[7, 23, 36, 44, 49, 55, 60, 63, 71, 74]
	Cardiac perforation	[7, 10, 11, 13, 15, 16, 23–25, 27–29, 31, 32, 35, 41, 51, 58, 59, 64, 74, 75]
	Allergic reaction	[61]
	Cardiac tamponade	[4, 10, 15, 16, 23, 26, 27, 37, 55, 56, 61]
	Chest pain	[14]
	Circulatory collapse	[35, 49, 55]
	Cardiac arrest	[62]
	Cardiac vein dissection	[4, 6, 35]

Frequency	Event Type	Reference ID
	Subclavian artery perforation	[59]
	Vascular injury (Total)	[4, 6, 35, 57, 59]
	Embolism (Total)	[24, 29, 36, 38, 55, 60]
	Implant site cellulitis	[10]
	Sepsis	[55, 64]
	Cerebrovascular accident	[10, 28, 55]
	Device connection issue	[4, 6, 7, 15, 17, 28, 32, 42, 51]
	Neurological symptom	[57]
	Arrhythmia (Total)	[7, 14, 30, 58, 59, 62]
	Pulmonary embolism	[55]
	Device deployment issue (Lead)	[7]
	Device deployment issue (Total)	[7, 15]
	Device deployment issue (RV-Lead)	[15]
	Implant site thrombosis	[4, 14, 26]
	Thrombosis (Total)	[4, 14, 15, 26, 28, 58, 65]
	Pacemaker generated arrhythmia	[7, 59]
	Pericarditis	[23, 55]
	Haemothorax	[4, 8, 24, 62, 63, 70, 76]
	Device battery issue	[4, 30]
	Embolism venous	[24, 29, 55]
	Atrial tachycardia	[14]
	Bacteraemia	[14]
	Complication of device insertion (RV Lead)	[7]
	Device electrical impedance issue (LV-Lead)	[7]
	Device programming error	[7]
	Myocardial infarction	[28, 55]
	Ventricular fibrillation	[62]
	Hot flush (during an MRI procedure)	[74]
	Implant site pain (during an MRI procedure)	[74]
	Implant site warmth (during an MRI procedure)	[74]
	Arrhythmia (Total, during an MRI procedure)	[78]
	Atrial arrhythmia (during an MRI procedure)	[78]
Improbable >(0.01%); ≤(0.10%)	Twiddler's syndrome	[17, 28, 68, 77]
	Implant site dehiscence	[51, 55]

Frequency	Event Type	Reference ID
Not known	Arteriovenous fistula	[8]
Frequency not assessable based on the available data	Embolism atrial	[55]
	Undersensing (RV)	[43, 69]
	Ventricular arrhythmia (during an MRI procedure)	[78]

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19.9 Reporting responsibilities

19.9.1 Reporting responsibilities of the investigator to sponsor

The investigator shall document and report all adverse events (AE) and serious adverse events (SAE), all adverse device effects (ADE) and serious adverse device effects (SADE) and all device deficiencies (DD) of BIOTRONIK products.

All events listed above shall be reported together with an assessment by completing the AE-CRF in accordance with ISO 14155:2020.

For device deficiencies of the investigational devices, 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 devices will be followed until local last-patient-out of the respective investigation site, but for a minimum of 4 weeks after 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 in some countries. Therefore as much information as possible should be provided to enable BIOTRONIK to explain the circumstances leading to the death. At least a pseudonymized copy of the death records and an autopsy report (if performed) should be sent to BIOTRONIK promptly. All actions taken, which were initiated to gain further information must be documented in writing and provided to BIOTRONIK.

19.9.2 Reporting responsibilities of the investigator to other parties

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

19.9.3 Reporting responsibilities of the sponsor

BIOTRONIK Australia Pty.Ltd. will report all serious adverse events (SAEs)/serious adverse device effects (SADE) and all device deficiencies with a SADE potential to the competent authorities depending on the local regulatory requirements.

Furthermore, BIOTRONIK Australia Pty.Ltd. and BIOTRONIK SE & Co. KG ensure 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 in a study newsletter. Unanticipated serious adverse device effects (USADEs) shall be reported immediately.

19.10 Reporting timelines

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

Table 5: Reporting timelines

Event	Report to	Timeline
Adverse event (AE) / adverse device effect (ADE)	CCR BIOTRONIK SE & Co. KG: Documentation in the AE CRF	Within 14 days
Serious adverse event (SAE) / serious adverse device effect (SADE)	CCR BIOTRONIK SE & Co. KG: Documentation in AE-CRF	Immediately, latest within 72 hours after awareness[5]
Unanticipated serious adverse device effect (USADE)	CCR BIOTRONIK SE & Co. KG: Documentation in AE-CRF	Immediately, latest within 72 hours after PI awareness
Device deficiencies	CCR BIOTRONIK SE & Co. KG: Documentation in the DD-CRF	Within 14 days
Device deficiency with SADE potential	CCR BIOTRONIK SE & Co. KG: Documentation in DD-CRF	Immediately, latest within 72 hours after awareness[5]

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 14155:2020. This obligation is not restricted to scheduled patient follow ups according to the CIP, but it is a continuous responsibility for the duration of the study, making sure that any unexpected risks originating from the study procedures or the investigational product are identified as soon as possible and patients are adequately protected. The principal investigator is responsible to set up appropriate workflows at his/her site, making sure that:

- the site study team is continuously informed on any relevant interactions or interventions concerning study patients at the site, regardless if members of the study team are directly involved or not;
- if the site is part of an organizational structure with departments and personnel beyond the study team, e.g. hospital or clinic, a process is in place, making sure that the study team has access and can monitor relevant events from other departments / clinics, such as hospitalizations;
- if information on relevant events from external sources reaches the site (e.g. medical reports from other facilities), these are made available to the study team without delay.

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

19.11 Return of investigational devices

Investigational devices which are related to a device deficiency or an adverse device effect must be returned to BIOTRONIK unless they remain implanted or in use. All explanted investigational devices must be returned to BIOTRONIK regardless of whether the explantation was related to an ADE or not.

19.12 Emergency contact

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

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

19.13 Data (safety) monitoring committee

Not applicable.

5 After investigation site study personnel´s awareness; If national legislation requires faster reporting the national requiremet shall be observed.

20 VULNERABLE POPULATION

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

The patient population of cardiac rhythm therapy consists predominantly of elderly people. Diagnostic and therapy methods are thereby adapted per se to this group of subjects. Considering this elderly population special attention is paid to patient information, patient consent and all study-specific examinations that are not included in routine care.

In case of incapacity acquired during study participation and either officially confirmed or assessed by the investigator, the patient should be excluded from study measures that go beyond routine care. Routine examinations / measurements or a further data collection can, however, be continued. The following study measures have been identified as going beyond routine care: the study follow-up schedule may deviate from the site´s routine follow-up schedule. However, the time windows are defined broadly so as to accommodate most routine visits. The activation of the features aATP or CRT AutoAdapt may have occurred due to study participation (see also section 9).

In the case of pregnancy, which is determined only after the start of study participation, the patient should be excluded from study measures that go beyond routine care. Routine examinations / measurements or a further data collection can, however, be continued. The following study measures have been identified as going beyond routine care: the study follow-up schedule may deviate from the site´s routine follow-up schedule. However, the time windows are defined broadly so as to accommodate most routine visits. The activation of the features aATP or CRT AutoAdapt may have occurred due to study participation (see also section 9).

In a pandemic situation, special care should be taken for above mentioned patients that study related follow-up visits that otherwise would have been canceled or postponed to avoid the risk of infection, are not conducted only for protocol compliance reasons (see section 6.5).

21 SUSPENSION

21.1 Criteria and procedures

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

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

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 investigation 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 investigation 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 investigation site.

21.2 Un-blinding procedures

Not applicable.

21.3 Requirements for patient follow-up and continued care

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

suspension is due to an EC 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 until local last-patient-out of the respective investigation site, but for a minimum of 4 weeks after study termination of the individual patient.

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

22 PUBLICATION POLICY

22.1 Decision for publication

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

All furthers decisions on publications will be made by the Publication Team, consisting of the coordinating investigator and member(s) of BIOTRONIK. In accordance with the good publication practice guidelines, it is generally planned to publish the study results also in case of negative findings. It is currently planned to submit at least an abstract to a congress or a manuscript within 12 months after finalization of the clinical investigational report.

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

22.2 Authorship guidelines

22.2.1 Purpose and validity

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

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

22.2.2 Authorship criteria

Following the International Committee of Medical Journal Editors (ICMJE), authorship credit should 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.

The Publication Team will assure a fair assessment of the contribution of all potential authors. Especially, the Publication Team will weight the contribution to the study data, and the contribution to the publication idea and content of all potential authors.

For *acquisition of data,* the following scoring system is valid:

- 1/2 point for each enrolled patient, plus
- 1 additional point for each patient, who is included in the data set for the analysis, plus
- 1 additional point for each patient with a complete and fully compliant data set until regular study termination according to the clinical investigational plan.

22.2.3 Authors' tasks and responsibilities

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

First author

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

Co-authors

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

22.2.4 Authorship of primary and ancillary publications

First authorship of the primary publication will be offered to the Coordinating Investigator. Investigators with the highest score will be considered for remaining positions.

The authorship of ancillary publications will be based on contribution to conception and design of the publication, analysis and interpretation of data, the score, and authorship on previous publications.

22.2.5 Timelines and compliance

The publication plan gives a detailed overview of timelines for preparation and submission of publications. If the first author will not provide a manuscript within appropriate time after a reminder, a co-author may be invited to become first author.

The Publication Team will ensure that authorship guidelines are met and authorship is attributed appropriately. The Publication Team will also track timeline adherence.

22.2.6 Reimbursement

No honoraria will be paid for authorship of publications.

22.3 Contributorship and acknowledgement

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

22.4 Ancillary publications

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

The Publication Team must approve ancillary requests and will need to ensure, that these publications do not present conflicts with other previously submitted requests. Requests for ancillary publications will be evaluated for scientific validity and the ability of BIOTRONIK to provide resources. All manuscripts and abstracts will be reviewed and approved by the coordinating investigator, all authors and BIOTRONIK.

Publication of single-center results will not be allowed until primary publication of the multicenter results. However, if such multicenter publication is not submitted within 12 months after conclusion or termination of the study at all participating centers, or after BIOTRONIK confirms there will be no multicenter publication, principal investigators may publish own data. However, the prinicpal investigator must provide to the Publication Team and to BIOTRONIK the intended publication not less than 1 month prior to planned submission.

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