AN EVALUATION OF THE SAFETY AND PERFORMANCE OF THE CATHVISION CUBE® SYSTEM

CLINICAL INVESTIGATION PLAN
CP-00003

24 March 2021

SPONSOR
CathVision ApS
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Document History Clinical Investigation Plan CP-00003

Version	Description	Release Date
A	Initial Release	27Mar2020
B	The following changes have been implemented: - Change of number of investigational sites - Added a new site in Denmark - Change of study start date - Clarification of the primary performance endpoint - Clarification of the primary safety endpoint - Additional information to the device description - Deletion of the physical examination and the vital signs - Clarification of anticipated adverse events with the CathVision Cube® System and the EP-procedures - Addition of malfunctions and device deficiencies from the CathVision Cube® System - Removal of the DMSB because it is not mandatory for this study - Improvement of the CIP structure - Implementation of the appendix 1-3 in the CIP - Minor wording changes	24Jun2020
C	The following changes have been implemented: - Adaption of study duration due to COVID-19 restrictions including start-and end date - Correction of timelines for Final Study Report - Added email address of PI Dr. Jacobsen - Administrative Changes	24Mar2021

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INVESTIGATOR'S AGREEMENT

I have read this Clinical Investigation Plan (CIP) and agree to adhere to the requirements. I will provide copies of this CIP and all pertinent information to all site personnel involved in this study. I will discuss this material with them and ensure they are fully informed regarding the products and the conduct of the study.

I agree to conduct the study as outlined in the CIP, in accordance with the signed study agreement and to the ethical principles stated in the latest version of the Declaration of Helsinki (2013), EN ISO 14155:2012 (Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice), or the applicable local and international regulations, whichever provide the greater protection of the individual. In addition, I agree to provide all the information requested in the Case Report Forms presented to me by the Sponsor in a manner to assure completeness, legibility and accuracy.

I also agree that all information provided to me by the Sponsor, including pre-clinical data, CIP, Case Report Forms, and any verbal and written information, will be kept strictly confidential and confined to the clinical personnel involved in conducting the study. It is recognized that this information may be relayed in confidence to the Ethics Committee and the Competent Authority.

In addition, no reports or information about the study or its progress will be provided to anyone not involved in the study other than the Sponsor, the Ethics Committee, and Competent Authorities (if applicable). Any such submission will indicate that the material is confidential.

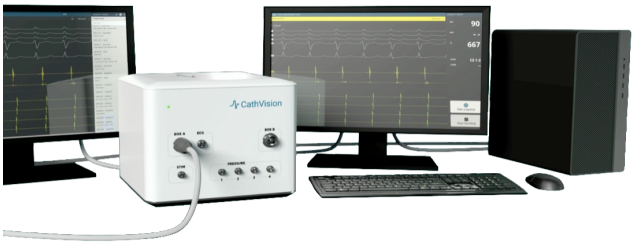
Principal Investigator's Name (print)

Title

Address

Signature / Date

STUDY SYNOPSIS

Title	An evaluation of the safety and performance of the CathVision Cube® System
Investigational Device	The CathVision Cube® System and accessories is an electrophysiology EP recording system to be used in EP procedures to acquire, amplify, digitize, stream atrial and ventricular intracardiac electrophysiology signals during cardiac electrophysiology procedures. 
Intended Use	Acquire, amplify, digitize, stream atrial and ventricular intracardiac electrophysiology signals during cardiac electrophysiology procedures.
Objective	The primary objective is to evaluate the safety and technical performance of the CathVision Cube® System. The secondary objective is to benchmark the intracardiac electrogram signal quality compared to commercially available systems in subjects undergoing elective assessment and ablation of cardiac arrhythmias (EP procedure).
Study Design	A prospective, multi-center, open-label, single arm study to evaluate the safety and technical performance of the CathVision Cube® System. Subjects who are indicated to undergo EP procedure and meet all inclusion criteria will be enrolled in the study and undergo the EP procedure. Intracardiac signals will be passively recorded using CathVision Cube® System in parallel with the commercial (CE marked) EP recording system. The investigational device will not be used for direct clinical care decisions or therapy. The EP procedure will be guided by the study site standards of care.
Sample size	Up to 30 subjects shall be enrolled in the study.
Investigational Sites	Two (2) investigational sites in Europe.
Study Duration / Follow-up Period	Study enrolment is planned from October 2020 to July 2021 Subjects will have clinical follow-up prior to hospital discharge.

Primary Performance Endpoint	The Primary Performance Endpoint of the study will be evaluated as technical success of CathVision Cube® System to collect and record intracardiac signals during EP procedures with focus on: • Recording low-voltage electrograms • Logging time for arrhythmia termination • Assessing the improved signal quality (baseline noise level peak-to-peak) • Assessing compatibility of CathVision Cube® System with a commercially available 3D mapping systems Biosense Webster Cart3 and GE Cardiolab. In addition, site standard of care available intracardiac catheters will be used.
Secondary Safety Endpoint	The Secondary Endpoint should demonstrate no or minimal adverse events or device malfunctions reported with the use of the CathVision Cube® System.
Enrollment Criteria	<u>Inclusion Criteria</u> Eligible subjects <u>will meet all</u> of the following inclusion criteria: 1. Patient indicated by investigator for catheter ablation or diagnostic electrophysiology procedure. 2. Male or non-pregnant female aged ≥18 years. Female subjects of childbearing potential must have a negative pregnancy test (per site standard test) within 7 days prior to index procedure. 3. Able and willing to directly provide informed consent. <u>Exclusion Criteria</u> Eligible subjects <u>will not meet any</u> of the following exclusion criteria: 1. Subject inability to understand or refusal to sign informed consent. 2. Pregnant or nursing subjects and those who plan pregnancy in the period up to 1 month following the index procedure. 3. Current participation in another investigational drug or device study that interferes with this study 4. Subject is a prisoner 5. Subjects who, in the opinion of the physician, are not candidates for this study.

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ABBREVIATIONS

ADE	Adverse Device Effect
AE	Adverse Event
AF	Atrial Fibrillation
ASD	Atrial Septal Defect
β-HCG	Beta Human Chorionic Gonadotropin
CA	Competent Authority
CIP	Clinical Investigatn Plan
CPK	Creatinine Phosphokinase
CS	Clinically Significant
CVA	Cerebrovascular Accident
CRA	Clinical Research Associate
CRF	Case Report Form
EC	Ethics Committee
ECG	Electrocardiogram
EGM	Electrogram
EP	Electrophysiology Procedure
GCP	Good Clinical Practices
GDPR	General Data Protection Regulation
LV	Left Ventricular
NCS	Not Clinically Significant
PFO	Patent Foramen Ovale
PI	Principal Investigator
PV	Pulmonary Vein
RF	Radiofrequency
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SW	Software
TIA	Transient Ischemic Attack
TEE	Transesophageal Echocardiogram
TTM	Trans telephonic Monitoring
UADE	Unanticipated Adverse Device Effect

1. Introduction

1.1. Cardiac Electrophysiology

Of the total worldwide population, 1% and 2% of rural and urban areas suffer from cardiac arrhythmia, respectively. Approximately 15% of patients do not respond to drug treatment and need a device-based interventional treatment. As a result, there is a great need of cardiac arrhythmia ablation. Today, however, the exact identification of the mechanism of the arrhythmia and subsequent successful ablation treatment are challenging for physicians. The three most prevalent arrhythmias ("complex arrhythmias") for catheter ablation are atrial fibrillation, atrial tachycardia and ventricular tachycardia.

1.2. Intracardiac electrophysiology signals during cardiac electrophysiology procedures

Cardiac electrograms are generated by the potential (voltage) differences recorded at two recording electrodes during the cardiac cycle. All clinical electrogram recordings are differential recordings from one source that is connected to the anodal (positive) input of the recording amplifier and a second source that is connected to the cathodal (negative) input. Unipolar recordings are obtained by positioning the exploring electrode in the heart and the second electrode (referred to as an indifferent electrode) distant (theoretically an infinite distance) from the heart such that it has little or no cardiac signal. Bipolar recordings are obtained by connecting two electrodes that are exploring the area of interest to the recording amplifier. At each point in time the potential generated is the sum of the potential from the positive input and the potential at the negative input. The potential at the negative input is inverted, and thus subtracted from that at the positive input. Because the far-field signal is similar at each instant in time, it is largely subtracted out, leaving the local signal. In a homogeneous sheet of tissue, the initial peak of the bipolar signal coincides with depolarization beneath the recording electrode. [2]

1.3. Rationale for this Clinical Investigation

Electrograms and their interpretation are a key tool for electrophysiologists to target ablation sites, and are acquired from electrodes on intracardiac diagnostic catheters and from surface ECG. Beside the dominant noise contributor of 50/60Hz from mains power line, there are noise contributors from stimulation, ablation and defibrillation artifacts that disturb the clear view of electrophysiological signals. Stimulation artifacts today are a result of (poor) software filter design, whereas ablation artifacts are mostly a hardware problem from the high energy exposure on the ablation tip electrode that is also used for measurements.

Baseline noise peak-to-peak levels below 15µV in bipolar recordings and below 30µV in unipolar recordings would be considered best-in-class. Bipolar recordings between adjacent band electrodes are the most commonly used and practically they are often "derived bipolar". This means they are individual signals first amplified against a different but common reference, and then subtracted from each other. Unipolar recordings are important for advanced algorithms, such as 3D mapping and rotor mapping for atrial fibrillation. The unipolar reference is most often Wilson Central Terminal (WCT), but it can also be a distant intracardiac electrode.

Electrograms are usually sampled at 1 to 2kHz, and bandpass filtered at 30 to 500Hz for bipolar and 0.5 to 300Hz for unipolar recordings. 64 to 160 channels are the typical capacity of recording systems today.

In the operating room, other devices and technologies are present: 3D mapping (triangulation of catheter tip position with impedance- and magnetic technology, <0.2 gauss), fluoroscopy/X-ray, RF generator, cryo gas station, stimulator, saline coolant pump for ablation catheter RF-tip irrigation, hemodynamics, magnetic catheter steering (0.08T).

It is not unusual to defibrillate the patient to cardiovert them from an arrhythmia. It is not unusual that patients have implanted defibrillators (ICDs).

It is CathVision's goal to develop a new electrophysiology recording system with improved signal quality particularly of unipolar recordings, with fast pacing and defibrillation recovery times, and with minimal or reduced RF ablation artifacts. The reduction in noise and artifacts will allow for better diagnosis and delivery of advanced ablation therapy in arrhythmia patients.

2. Device Description

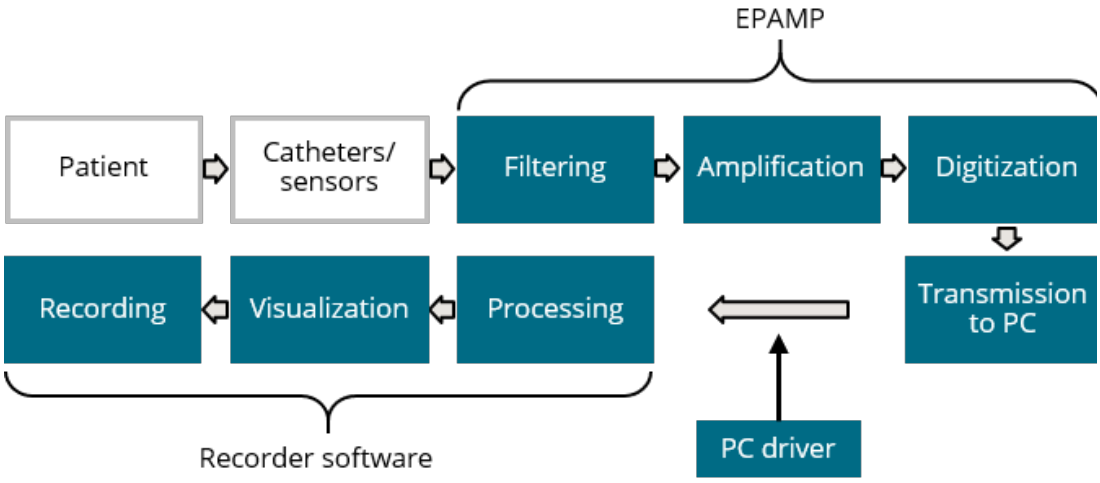
The CathVision Cube® System is an electrophysiology (EP) recording system used in EP procedures as a tool to monitor, display, and record signals of the heart and cardiac arrhythmias. The CathVision Cube®System includes the following items:

- EP amplifier (EPAMP)
- Pin box cable assembly for connection of catheters
- Surface ECG cable
- Data cable to host computer
- Recording system software (RECORDER SW)
- Host computer (PC) and monitors

Additional information involving the device and its components, including all preclinical and clinical test results, can be found in the Investigator's Brochure or in the Instructions for Use.

2.1. Signal Processing Overview

The main hardware amplifier of the CathVision Cube® System is the EPAMP, which acquires signals from third-party catheters and sensors connected to the subjects. It then sends the signals to the CathVision Cube® System, which has a software program called the RECORDER SW that visualizes the signals to the user and provides the users a way to interactively analyze them. The following figure illustrates this signal pathway.



There are no parts of the CathVision Cube® System that may come into contact with subjects body or body fluids.There are no medicinal products, human or animal tissues or their derivatives, or other biologically active substances used in the device.

2.2. Device Labelling

The investigational device does not have a CE label, therefore the study device will be labelled "for investigational use only".

Each manufactured investigational device is assigned a unique serial or lot number that is printed on the device labeling, providing a means of traceability. A device accountability log will be used to track the use of devices in the study. The serial number will be recorded on each case report form

3. Risk-Benefit Analysis

There are no known risks to the potential subjects specifically associated with the use of the CathVision Cube® System.

Potential subject risks include adverse events and potential product failures similar to commercially available EP recording systems, with a similar likelihood of occurrence.

Potential device malfunctions and potential user errors have been identified in the Hazard Analysis and Failure Modes and Effects Analysis exercises conducted in accordance with ISO 14971. These are technical complications that may occur with the devices. Mitigating steps to address each of the potential device malfunctions and potential user errors have been implemented to reduce the risks as low as possible. No residual risks remain that are higher than the risks associated with the use of currently available conventional cardiac electrophysiology and catheter ablation tools. A list of device deficiencies and malfunction are defined in section 7.7 of this document.

The anticipated adverse events associated with cardiac electrophysiology procedures include events reported in the literature related to catheter procedures, events identified in the risk and hazard analyses, and events associated with percutaneous interventions, and therefore represent the risks associated with participation in the study. A list of anticipated adverse events is defined in Section 7.6 of this document. Each adverse event or device effect will be evaluated in detail as described in Section 7 of this document.

The CIP is designed for parallel data collection during electrophysiology study and investigator diagnostic decisions will be guided by an approved EP recording system. Due to this CIP design and noninvasive nature of the tested medical device there is expected a low rate of occurrence of SAEs or SADEs related to use of investigational device. CathVision personnel will be responsible for operation and installation of the tested device.

The potential patient benefits include reduction in symptomatic episodes of arrhythmia due to possible better interpretation of EP signals using the CathVision Cube® system. As the treatment will be guided by an approved EP recording system the reduction in symptomatic arrhythmia will be similar to the benefit of currently available EP recording systems.

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4. Clinical Investigation Plan (CIP)

4.1. Study Objectives

The primary objective is to evaluate the safety and technical performance of the of the CathVision Cube® System. Secondary objective is to benchmark the intracardiac electrogram signal quality compared to commercially available systems in subjects undergoing assessment and ablation of cardiac arrhythmias.

4.2. Study Design

A prospective, multi-center, open-label, single arm study to evaluate the safety and technical performance of the CathVision Cube® System.
Subjects who are indicated to undergo EP procedure and meet all inclusion criteria will be enrolled in the study and undergo EP procedure using an approved EP system in conjunction with the CathVision Cube® System. Intracardiac signals will be passively recorded in parallel with the commercial (CE marked) EP recording system. The investigational device will not be used to direct clinical care decisions or therapy. The EP procedure will be guided by study site standards of care.

4.3. Study Duration

Study enrolment is planned from October 2020 to July 2021
Subjects will have clinical follow-up prior to hospital discharge.

4.4. Subject Population

Up to 30 subjects shall be enrolled in the study at a single site meeting the following study entry criteria will be treated.

4.4.1. Inclusion Criteria

Eligible subjects will meet all of the following inclusion criteria:

1. Subject indicated by investigator for catheter ablation or diagnostic electrophysiology procedure.
2. Male or non-pregnant female aged ≥18 years. Female subjects of childbearing potential must have a negative pregnancy test (per site standard test) within 7 days prior to index procedure.
3. Able and willing to directly provide informed consent.

4.4.2. Exclusion Criteria

Eligible subjects will not meet any of the following exclusion criteria:

1. Subject inability to understand or refusal to sign informed consent.
2. Pregnant or nursing subjects and those who plan pregnancy in the period up to 1 month following the index procedure.

3. Current participation in another investigational drug or device study that interferes with this study.
4. Subject is a prisoner.
5. Subjects who in the opinion of the physician are not candidates for this study. Prior atrial septal defect (ASD) or patent foramen ovale (PFO) closure with a device using a transcatheter percutaneous approach.

5. Study Outcomes

5.1. Primary Performance Outcome

The Primary Performance Endpoint of the study will be evaluated as technical success of CathVision Cube® System to collect and record intracardiac signals during EP procedures with focus on:

- Recording low-voltage electrograms
- Logging time for arrhythmia termination / block
- Assessing the improved signal (baseline noise level peak-to-peak)
- Assessing compatibility of CathVision Cube® System with a commercially available 3D mapping systems Bioscience Webster Carto3 and GE Cardiolab. In addition, site standard of care available intracardiac catheters will be used.

5.1.1. Primary Safety Outcome

The Secondary Endpoint of the study should demonstrate no or minimal adverse events or device malfunctions reported with the use of the CathVision Cube® System.

5.2. Study Procedures

Following is a detailed list of study visits from screening to discharge and the required procedures/tests.

5.2.1. Informed Consent

Prior to recruitment of any subjects into the study, written approval of the CIP and informed consent must be obtained from the Ethics Committee (EC) and Competent Authority (CA).

Pre-screening, i.e., medical record review without obtaining informed consent, is allowed.

Informed consent must be obtained from each subject prior to conducting any study-related tests or procedures, including screening procedures.

The investigator will explain the study purpose, procedures, and subject's responsibilities to the potential participant. The subject's willingness and ability to meet the study requirements will be determined, and written informed consent will be obtained. The subject will sign and date the informed consent form. The investigator will also sign and date the consent form. The

original informed consent form will be retained with the subject records. A copy of the informed consent will be provided to the subject.

A subject is considered enrolled after informed consent has been obtained.

5.2.2. Subject Identification

To maintain confidentiality, the subject's name will not be recorded on any study document other than the informed consent form. Each enrolled subject will be pseudonymized and assigned a unique identifier in the following format: CCC-SSS-PPP. CCC is the Country code (same as Tel.) SSS is the site number and PPP is the 3-digit sequential subject ID number starting with 001. For example, the first subject in CZ at site 001 will be assigned 420-001-001. Subject ID numbers will not be re-used (e.g., if the subject is determined to be a screen failure).

5.3. Study Visits

5.3.1. Schedule of Assessments and Visits

	Visit 1 Screening Max 30 days before index EP procedure	Visit 2 Index EP procedure	Visit 2 Discharge
Informed Consent	✓		
Demographics	✓		
Cardiac Medical History	✓		
Arrythmia History	✓		
Cardiac Medications	✓	✓	✓
Inclusion/Exclusion	✓		
12 lead ECG	✓		✓
Urine Pregnancy Test*	✓		
EP procedure		✓	
Adverse Events		✓	✓
Device Malfunctions		✓	
Protocol Deviations	✓	✓	✓

* Women of child-bearing potential only Max 7 days before Index EP Procedure (Visit 2

5.3.2. Visit 1: Screening Visit

Screening will be completed within 30 days of the index EP procedure date.

Test results from routinely performed standard assessments may be used to determine eligibility. Pre-screening will consist of a review of relevant medical history including duration and frequency of arrhythmia(s), their subsequent treatments (e.g., medications, previous ablation) and associated symptoms.

If pre-screening criteria are met, informed consent will be obtained, and screening will proceed. Eligibility will be assessed sequentially, starting with the least invasive and least expensive tests as follows. Results from each test or screening activity should be reviewed prior to proceeding to the next step.

- Demographics
- Cardiac medical history
- Arrhythmia history (TTM, EKG, Holter, etc.)
- Cardiac medications
- In / Exclusion criteria
- 12-lead ECG
- Pregnancy test (pre-menopausal women only, within 7 days of index EP procedure)
- Protocol deviations
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5.3.3. Screen Failures

Subjects not meeting all study entry criteria will be designated as screen failures. End of study procedures will not be performed for these subjects, but their reason for ineligibility will be recorded on the Screening Log. Screen failures are counted towards the total study enrollment.

5.3.4. Visit 2: Index Procedure through Discharge

During the index EP procedure, only procedures or steps from institutional standard of care / best practice will be used to treat the subjects.
When the subject is connected to the standard EP recording system, during manipulation of catheters or diagnostic tests, intracardiac signals will be recorded using the investigational device in parallel. It is not expected to cause any significant delays to the total procedure time as the final comparison of data recorded from Standard EP recording system and the tested device will happen post procedure.

Index EP procedure, the following will be documented

- EP data recording
- Change in cardiac medication
- Adverse events and device malfunctions
- Protocol deviations

Prior to discharge, the following will be documented:

- 12 lead ECG will be performed
- Change in cardiac medications
- Adverse events
- Protocol deviations

All subjects will exit the study after this visit.

5.4. Study Completion

5.4.1. Completed Subjects

Subjects will be considered complete when all assessments through the Discharge have been performed in accordance with the CIP.

5.4.2. Discontinued Subjects

Any subject may voluntarily discontinue the study at any time without prejudice. The investigator may discontinue a subject from the study at any time if (s)he considers that remaining in the study compromises the subject's health or the subject is not sufficiently cooperative. In either event, reason(s) for discontinuation should be recorded.

Possible reasons for study discontinuation include the following:

- Adverse events (AEs) necessitating discontinuation from the study
- Subject decision (specify
- Investigator decision (specify)
- Other reason (specify)

The reasons for any subject discontinuation will be recorded on the study completion form of the study CRF. If possible, subjects who withdraw prior to study completion will undergo the following:

- AE assessment
- Device malfunction, if applicable

5.4.3. Premature Study Termination

The Sponsor, Investigators, Ethics Committee, or Competent Authority have the right to suspend or terminate the study prematurely for any safety, ethical or administrative reason at any time.

The study will be suspended or prematurely terminated if, in the opinion of the Principal Investigator (PI), Sponsor, reviewing EC or Competent Authority, the safety of subjects and/or data is uncertain. The Sponsor should make sure that the suspension or prematurely termination will be communicated through the PI, Competent Authority and reviewing EC.

Possible reasons for suspending/terminating a study center include but are not limited to:

- Failure to obtain written Informed Consent
- Failure to report SAEs/SADEs to Sponsor within 24 hours of knowledge
- Loss of (or unaccounted for) investigational product inventory
- Repeated protocol deviations
- Repeated failure to complete case report forms prior to scheduled monitoring visits

In the event of premature study termination, a written statement as to why the premature termination has occurred will be provided to the study site by CathVision ApS. The EC and the Competent Authorities will be notified. Detailed information on how enrolled subjects will be managed thereafter will be provided.

In the event an EC terminates participation in the study, participating study site and Competent Authorities will be notified in writing. Detailed information on how enrolled subjects will be managed thereafter will be provided by CathVision ApS.

In the event the investigator terminates participation in the study, study responsibility will be transferred to a co-investigator when possible or another authorized Investigator. In the event there are no opportunities to transfer investigator responsibility; detailed information on how enrolled subjects will be managed thereafter will be provided by CathVision ApS (Sponsor).
The investigator must return all documents and investigational product to Sponsor, unless this action would jeopardize the rights, safety, or welfare of the subjects.
Sponsor reserves the right to stop the inclusion of subjects at a study site at any time if no subjects have been enrolled for a period beyond 3 months after the site has been granted approval to enroll, or if the study site has multiple or severe protocol deviations/noncompliance without justification and/or fails to follow remedial actions.
In the event of termination of investigator participation, all study-related devices and equipment, as applicable, will be returned to Sponsor unless this action would jeopardize the rights, safety or well-being of the subjects. The EC and Competent Authorities will be notified.

5.5. Investigational Device Accountability

Documentation of receipt, use and return of the CathVision Cube® System and its parts must be maintained by the Principal Investigator (PI) or his/her Designee in a device accountability log. Investigational devices are to be used only in accordance with this CIP and under supervision of the PI or a duly designated person. It is the PI's responsibility to ensure that all study devices are kept in a secure location, with access limited to individuals authorized by the investigator. A record of all study devices (by their lot or serial numbers) received, used and returned must be maintained by the site until the conclusion of the study. Following accountability of the study devices by the Sponsor or its Designee, all unused study devices will be returned to the Sponsor/Designee as directed in writing by the Sponsor or Designee for gross reconciliation.

6. Examinations and Evaluations

6.1. Demographics

Date of birth, gender, race and ethnicity will be recorded.

6.2. Cardiac and Arrythmia Medical History

Relevant cardiac and arrythmia medical history including duration and frequency of arrhythmia(s), their subsequent treatments (e.g., medications, previous ablation) and associated symptoms will be obtained at Screening. All positive and negative findings will be carefully documented. Any new finding discovered during the Screening evaluation and prior to the index EP procedure will be considered to be part of the medical history and will not be recorded as an AE.

6.3. Cardiac Medications

Cardiac medications (including antiarrhythmic drugs) will be recorded at each visit, including medications prior to the visit and medications prescribed during the visit. For each medication, the following information will be collected:

- Medication trade or generic name

- Indication for which the medication was given
- Dose/strength, route, and frequency of administration
- Date started
- Date stopped (or continuation at study exit)

6.4. 12-Lead ECG

A 12-lead electrocardiogram (ECG) will be conducted. The ECG recording will be printed out, and a copy will be placed with subject records. Any clinically significant abnormalities will be recorded.

6.5. Pregnancy Test (women of childbearing potential only)

For women of childbearing potential, a urine beta human chorionic gonadotropin (β-HCG) test will be performed at Screening, and again if undergoing a remapping procedure. Results of the test must be negative. Confirmed menopause is defined as postmenopausal for ≥ 1 year.

7. Safety Reporting and Device Deficiencies

7.1. Adverse Events Definitions

An **adverse event (AE)** is the development of an untoward medical occurrence or the deterioration of a pre-existing medical condition following or during exposure to an investigational medical device, whether or not considered causally related to the investigational medical device.

An untoward medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or clinically significant abnormal results of an investigation (e.g., laboratory findings, electrocardiogram).

Conditions or diseases that are chronic but stable should not be recorded as an AE. Changes in a chronic condition or disease that are consistent with natural disease progression are NOT considered AEs and should not be recorded. These medical conditions should be adequately documented in the subject's medical history. However, medical conditions present at enrollment that worsen in intensity or frequency in a manner inconsistent with the natural course of the disease during the treatment or post-treatment periods should be reported and recorded as AEs.

A recurrence of an atrial tachyarrhythmia requiring hospitalization in order to administer cardioversion within the blanking period is within the scope of treatment for chronic but stable AF subjects. This will not be considered an adverse event. Self-limiting pericarditis attributable to the EP procedure, defined as pleuritic chest discomfort with or without pericardial rub and ECG changes, is not considered an adverse event.

A **serious adverse event (SAE)** is any untoward medical occurrence which:

- Results in death, permanent impairment of a body function or permanent damage to a body structure;

- Results in serious deterioration in the subject's health that either:
    - Is life-threatening;
    - Requires inpatient hospitalization (admission to hospital with a stay > 24 hours) or prolongation of hospitalization which is not specifically required by the CIP or is elective;
    - Results in permanent impairment of a body function or permanent damage to a body structure; or
    - Requires medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

Additionally, important medical events that may not result in death, be life-threatening or require hospitalization may be considered SAEs when they jeopardize the subject or require medical or surgical intervention to prevent one of the serious outcomes listed above.

Adverse device effect (ADE) is an AE related to the use of an investigational medical device. Note, this definition includes AEs resulting from insufficient or inadequate instructions for use, operation, or any malfunction of the investigational medical device. In addition, this definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

Serious adverse device effect (SADE) is an ADE that that has resulted in any of the consequences characteristic of a SAE.

An **unanticipated adverse device effect** (UADE) is defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in predicate devices, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

7.2. Assessment of Adverse Events

The need to capture AEs is not dependent upon whether or not the clinical event is associated with the use of the study device or procedure. All AEs, regardless of severity, occurring at the index EP through study exit visit must be recorded. Events occurring prior to the endovascular procedure must be listed in the medical history.

Any Adverse Event(s) that may occur in this study needs to be reported directly to the Sponsor and the EC, as applicable. Participants experiencing Adverse Events must be treated by the investigator per clinical standard practice at the hospital.

The following information should be obtained for each AE:

1. **Event description.** Every effort must be made to report the underlying condition or unifying diagnosis for the event. To avoid vague, ambiguous or colloquial expressions, the AE should be recorded in standard medical terminology rather than the subject's own words when possible. Signs and symptoms that are considered unrelated to an encountered syndrome or disease should be recorded as individual AEs on the CRF (e.g., if congestive heart failure and severe headache are observed at the same time, each event should be recorded as an individual AE).

In addition, AEs occurring secondary to other events (e.g., sequelae) should be identified by the primary cause (i.e., a "primary" AE, if clearly identifiable, generally represents the most accurate clinical term to record on AE CRF; events occurring secondary to the primary event should be described in the narrative description of the case [e.g., example: orthostatic hypotension → fainting and fall to floor → head trauma →neck pain; the primary AE is orthostatic hypotension]).

2. **Duration:** The date of onset and date of resolution should be reported. Every effort should be made to capture the exact dates.

3. **Outcome:** The final status of the event should be reported as resolved, ongoing, or if it resulted in death. If the event is present at the final study visit, the ongoing box must be marked.

4. **Severity:** The worst severity of the event must be reported as mild, moderate, or severe using the following definitions:

    - **Mild:** Aware of sign or symptom, but easily tolerated
    - **Moderate:** Discomfort enough to cause interference with usual activity
    - **Severe:** Incapacitating with inability to work or do usual activity

5. **Action taken**: Treatment of the event may be reported as none, medical and/or surgical.

6. **Seriousness:** Determined by using the criteria in Section 7.1.

7. **Relationship to device (study device or ancillary device), and procedure.** The relationship to device and study procedure will be assessed using the following criteria.

    - **Not related:** no temporal association, or the cause of the event has been identified; or the device or procedure cannot be implicated
    - **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:** temporal association, but other etiologies are likely to be the cause; however, involvement of the device or procedure cannot be excluded
    - **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:** temporal association; other etiologies are possible, but unlikely

    If any AE is considered to be “possibly related” or “related” to the use of the study device, that event will be classified as an ADE or a SADE.

7.3. Reporting/Recording of AEs

Throughout the course of the study, all efforts will be made by the investigator to remain alert to possible AEs. The first concern will be the safety of the subject, and for providing

appropriate medical intervention. The period of observation for collection of AEs starts at index EP procedure until study exit. Any AE should be recorded on the appropriate study CRF.

7.4. Adverse Events Requiring Expedited Reporting

7.4.1. Investigator Responsibilities

The Investigator is responsible for reporting all SAEs, SADEs, and device deficiencies that could have led to a SADE to the EC, according to national regulations and EC requirements. The investigator will forward a copy of this report to the Sponsor and file it in the investigator site binder.

The Investigator will document all SAEs and SADEs, including device deficiencies in the study subject's file and report it to the Sponsor and to the Sponsor's (Designee) within 24 hours of knowledge of event. When medical reports (lab results, examinations, etc.) associated with AEs are submitted to the Sponsor or Sponsor's Designee, all personal subject information (name, address, etc.) ***must*** be removed or redacted. The redacted materials must be identified only with the subject ID number.

In the event of a subject's death, the Investigator will make reasonable effort to obtain a copy of the autopsy report and/or death summary. The Investigator will determine the cause of death and its relationship to the investigational device; the Investigator will record results on the AE case report form (CRF). The Investigator will include copies of an autopsy report, if available, and/or a death summary with this form.

7.4.2. Sponsor Responsibilities

Upon notification of SAEs, the Sponsor will initiate and complete a review and evaluation of the event within time frames that will maintain reporting compliance with applicable regulatory agencies. The Sponsor is responsible for classification and reporting of AEs and ongoing safety evaluation of the clinical investigation in line with EN ISO 14155:2012 and regulatory requirements. If insufficient information is available to reach a definitive diagnosis, the Sponsor may instruct the CRA responsible for the site to contact the site to request additional confirmatory information, if any.

The Sponsor will ensure that its Designee will report all SAEs and device deficiencies that could have led to an SADE to the Competent Authorities in accordance with European Medical Devices Directive and all applicable national regulations including the medical device act of the Czech Republic and Denmark.

7.5. Anticipated Adverse Events Related to the CathVision Cube® System

There are no anticipated Adverse Events specifically associated with the use of the CathVision Cube® System or similar CE-labelled EP recording devices currently available.

7.6. Anticipated EP-Procedure Adverse Events

Anticipated complications/AEs are defined as complications/events that can be reasonably associated with the EP catheter ablation procedures. The mitigations and treatments for these AEs will follow published guidance for the same AEs occurring with other commercially available devices [1].

Anticipated AEs include, but are not limited to:

- Air embolism
- Allergic reaction (including anaphylaxis)
- Anesthesia reaction
- Angina
- Aorto-right atrial fistula
- Arrhythmias, including exacerbation of pre-existing atrial fibrillation
- Arterial-venous fistula
- Cardiac perforation/ tamponade
- Cardiac thromboembolism
- Cardiac or respiratory arrest
- Catheter entrapment
- Cerebrovascular incident / Stroke
- Chest pain/discomfort
- Congestive heart failure
- Coronary artery dissection
- Coronary artery spasm
- Coronary artery thrombosis / occlusion
- Death
- Diaphragmatic paralysis
- Endocarditis
- Esophageal ulceration
- Gastroparesis
- Heart failure / pump failure
- Hemoptysis
- Hemoptysis
- Hemothorax
- Hypotension
- Hospitalization (initial and prolonged)
- Increased creatinine phosphokinase (CPK) level
- Infections
- Laceration
- Leakage of air or blood into the lungs or other organs due to perforation
- Left atrial esophageal fistula
- Major bleeding, requiring surgery or transfusion
- Myocardial infarction
- Obstruction or perforation or damage to the vascular system
- Pericarditis
- Pericardial effusion
- Phrenic nerve damage including Diaphragmatic paralysis

- Pleural effusion
- Pneumonia
- Pneumothorax
- Pulmonary edema
- Pulmonary embolism
- Pulmonary vein dissection
- Pulmonary vein thrombus
- Pulmonary hypertension
- Respiratory depression
- Skin burns
- Severe PV stenosis or complete occlusion, even asymptomatic
- Tamponade, potentially requiring surgery
- Temperature elevation or fever
- Transient Ischemic Attack (TIA)
- Thromboembolism
- Thrombosis
- Unintended complete or incomplete AV, Sinus node, or other heart block or damage
- Valve damage
- Vascular bleeding / local hematomas / ecchymosis
- Vasovagal reactions
- Ventricular tachyarrhythmia
- Volume overload

7.7. Device Deficiencies

Device deficiency is defined as an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.

Note, device deficiencies include malfunctions, use errors, and inadequate labelling. All device deficiencies or malfunctions that occur during the course of the study and could have led to an SAE must be reported, whether or not they were associated with an AE.

Device malfunction: failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use.

User error: act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user.

The Device Deficiency CRF is specific for reporting all device deficiencies, or malfunctions that occur during the course of the study, whether or not they were associated with an adverse event. Device Deficiency CRFs should be submitted to the Sponsor within 24 hours of the occurrence defining the device deficiency.

Anticipated device deficiencies and malfunctions include but are not limited to:

- Catheter deflection deficiency or failure
- Malfunction of a catheter electrode

- Malfunction of a catheter temperature sensor
- Unexpected termination of ablation due to internal system error
- Failure to initiate ablation due to internal system error
- Temporary or sustained loss of catheter navigation/visualization capability/signal

Record any CathVision Cube® System deficiencies and malfunctions including but are not limited to:

- CathVision Cube® System issues (EPAMP/RecSW)
  - Not able to power on
  - Power indicators not on
  - Not able to connect to the standard of care EP system
  - Note able to retrieve signal from standard of care EP system
  - Not able to power down
  - Database issues
  - Backup data issues
  - Not possible to clear fault without reboot
  - CathVision Cube® System Recorder Software
  - Malfunction
  - Loss of power
  - Loss of wave form
  - Recording issues (interruption, stop)
    - Not able to create patient
    - Not able to save patient
    - Live Mode issues (not able to create/resume patient, etc.)
    - Review Mode issues (not able to retrieve a patient)
    - SW crashes
    - SW loses connection to EPAMP
    - Limitation: Only possible to review the latest recording file, while streaming is active
    - Bug: Not possible to use the notch filter, if high-pass and low-pass is set to 'None'

- Host Computer Malfunctions
  - Not able to boot/start

- User errors

8. Statistical Methods

8.1. Sample Size Calculation

This study is intended to demonstrate safety and performance of the device. As a result, no formal statistical hypothesis was applied to derive the sample size. A drop-out rate is expected to be low due to acute and low risk profile of CIP.

8.2. Descriptive Analyses

Continuous variables will be summarized using standard quantitative statistics: number of non-missing observations, mean, standard deviation, median, quartiles and range (minimum and maximum observed values). The number of missing observations, if any, will also be summarized.

Categorical variables will be summarized using classical frequency statistics: number of non-missing observations and percentages by categories. Number and percent of missing data, if any, will also be summarized.

There are no predefined criteria for terminating the study based on statistical outcomes. Missing data will not be replaced or imputed.

9. Compliance

9.1. Ethics Committee (EC)

Prior to the initiation of the study, the CIP, and the informed consent form will be submitted to the EC for approval. By signing the Clinical Study Agreement, the investigator is assuring that an EC will be responsible for the initial and continuing review of the proposed study. A copy of the EC approval letter for the CIP, the informed consent, and the CIP signature page must be submitted to the Sponsor or its Designee prior to release of investigational supplies to the study site. The approval letter must refer to the specific CIP and the informed consent form. Any Investigator who is also a member of the EC is not to participate in the study approval decision. This non-participation must be noted in the approval letter. The study site must maintain an accurate and complete record of all reports, documents and other submissions made to the EC concerning this CIP.

Any report of withdrawal of EC approval will be submitted to the Sponsor or its Designee within five (5) working days.

9.2. Competent Authority (CA)

The study will be reviewed by the relevant Competent Authority as well. The Sponsor or its Designee is responsible for obtaining regulatory approval for the study from the relevant Competent Authority. No subjects may be enrolled in the study until written notification of such approval has been given by the Sponsor. The Sponsor or its Designee is responsible for reporting SAE and Device Deficiencies that might have led to a SADE as appropriate to the

relevant Competent Authority. The Sponsor or its Designee is responsible to provide the relevant Competent Authority with the study final report within 90 days of the study termination.

The study will not start without the written approval of the EC and the Competent Authority.

9.3. Good Clinical Practice Statement

This study will be conducted in compliance with the CIP, the signed Clinical Study Agreement and with the ethical principles stated in the latest version of the Declaration of Helsinki (2013), the applicable guidelines for good clinical practices, MEDDEV 2.7/4 (Guidelines on Clinical investigations: a guide for manufacturers and notified bodies) and 2.7/3 (Clinical investigations: serious adverse event reporting), EN ISO 14155:2012 (Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice), and the applicable local and international regulations, in order to provide the greatest protection of the individual. Any deviations from the CIP that may affect the safety and welfare of study participants will be immediately reported to the Sponsor and to the Ethics Committee (EC) per each institution's guidelines.

9.4. Investigator Responsibilities

The Principal Investigator of an investigational site is responsible for ensuring that the study

is conducted in accordance with the Clinical Study Agreements, the CIP, ISO 14155:2012, ethical principles that have their origins in the Declaration of Helsinki, any conditions of approval imposed by the reviewing EC, and prevailing local and/or country laws and/or regulations, whichever affords the greater protection to the subject. In addition, the Investigators are responsible for:

- Ensuring that the study is conducted with the express approval of the CA/EC
- Ensuring that conducting the study will not give rise to conflicts of interest
- Ensuring that informed consent is obtained appropriately and that the conditions of informed consent are complied
- Ensuring that all subjects entering the study conform with the Clinical Investigation Plan
- Ensuring to compliant with the CIP
- Ensuring the appropriate completion of all CRFs
- Maintaining all records as described in the CIP and according to the national guidelines and laws and the institutions requirements
- Ensuring the documentation, maintenance and correctness of the device accountability
- Ensuring that all investigational study material needs to be returned to the Sponsor at the end of study
- Informing the Sponsor of all adverse events and adverse device effects in a timely manner and informing the EC of any serious adverse device effects as applicable
- Informing the Sponsor in writing of the reason(s) for any withdrawal of any CA/EC approval

- Ceasing the enrollment of subjects immediately in the event of the withdrawal of any CA/EC approval
- Agreeing to use their best efforts to satisfactorily complete the planned work and to comply at all times with accepted Good Clinical Practice
- Informing the Sponsor of any conditions under which prior research was terminated
- Supporting the CRA, Auditor and the Sponsor's Designee (as applicable) in their activities

9.5. Sponsor Responsibilities

All information and data sent to the Sponsor concerning subjects or their participation in this study will be considered confidential. Only authorized Sponsor or Sponsor's Designee will have access to these confidential records. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this study. Study data collected during this study may be used by the Sponsor for the purposes of this study, publication, and to support future research and/or other business purposes. All data used in the analysis and reporting of this study will be without identifiable reference to specific subject name and will be pseudonymized. The Sponsor or authorized Designees of the Sponsor may be present at the EP procedures to provide technical and study specific assistance and shall assist with the collection of recorded technical data via the use of Technical Source Forms. The CathVision Cube® System is password protected and only the Sponsor is allow to work with the study device. Any data collected by the Sponsor's Designee will be verified and counter signed by the Investigator. The Sponsor's Designee will not:

- Practice medicine
- Provide medical diagnosis or treatment to subjects

9.6. Clinical Investigation Plan Amendments

The Sponsor will document modifications to the CIP in the form of a written amendment, with updated version identification. All CIP modifications must be approved by the CA/EC before implementation.

10. Study Conduct

10.1. Informed Consent Process

It is the responsibility of the Investigator to inform each subject prior to the screening evaluation, of the purpose of this study, including possible risks and benefits and document the informed consent process in the subject's chart. Any changes made to the informed consent must be approved by the Sponsor or its Designee, prior to submission to an EC. After approval by the Sponsor or its Designee, the informed consent must be submitted to and approved by the applicable EC.

The process of obtaining informed consent at a minimum shall include the following steps:

- Ensure that the principal investigator or its authorized Designee conducts the informed consent process
- Include all aspects of the clinical investigation that are relevant to the subject's decision to participate throughout the clinical investigation
- Avoid any coercion or undue improper influence on, or inducement of, the subject to participate
- Not waive or appear to waive the subject's legal rights
- Use native non-technical language that is understandable to the subject
- Provide ample time for the subject to read and understand the informed consent form and to consider participation in the clinical investigation
- Include personally dated signatures of the subject and the principal investigator or an authorized Designee responsible for conducting the informed consent process
- Provide the subject with a copy of the signed and dated informed consent form and any other written information
  Ensure important new information is provided to new and existing subjects throughout the clinical investigation

One original informed consent form is to be retained by the study site and a copy is to be given to the subject. The informed consent process must be documented in the subject's source/medical record.

The informed consent must be written in a language in which the subject is fluent. If a foreign language translation is required, a statement of certification of the translation must be issued. Regulations require that foreign language informed consent forms be submitted to the EC for approval. The investigator must forward a copy of the consent form, the certified foreign language translation and an EC approval letter to the Sponsor or its Designee.

10.2. Study Training

Each study site will undergo a study initiation visit including but not limited to a review of the following:

- CIP
- Study Procedures and Assessments
- Process for obtaining Informed Consent and completing Informed Consent Form
- Reporting requirements
- Case Report Form (CRF) completion and Good Documentation Practices

- Study device overview, usage, and accountability
- Protection of patient confidentiality

10.3. Study Monitoring and Source Document Verification

The Sponsor or its Designee may meet with investigators prior to the initiation of the study in order to review the adequacy of the subject population, facilities, and equipment with respect to the needs of the study, and to familiarize the investigator with the CIP.

During the study, the CRA will visit the study facilities regularly and utilize telephone and written communications on an ongoing basis to maintain current knowledge of the study. During periodic visits to the study site, the CRA will review the source documents used for completion of the CRFs to verify the accuracy and completeness of the information contained in those reports in preparation for retrieval. Source documents must contain all data entered in the CRFs. Source documents may include a subject's medical record, hospital charts, clinic charts, the Investigator's study files, the results of diagnostic tests such as laboratory tests, EKGs, 24-hour Holter monitoring and the like. All data generated during this study and the source documents from which they originated are subject to inspection by the Sponsor or its Designees and/or regulatory agencies.

Subject safety will be ensured by noting that the consent was properly documented, the CIP was followed, and that AEs were reported and followed-up as appropriate.

The CRA will evaluate and summarize the results of each clinical site visit in written reports, identifying any repeated data problems with any Investigator and specifying recommendations for resolution of noted deficiencies.

As required by the ISO 14155:12, the conduct and monitoring of the clinical investigation will be conducted in accordance with the Sponsor's approved monitoring plan.

10.4. Study Close-out

Upon completion of the study, the CRA will conduct a final visit (close-out) to the site. The objectives of this visit are to ascertain that all regulatory records and reports are complete, verify that investigational devices and other supplies have been accounted for and ensure that the investigator is aware of his/her responsibilities post-study. The observations and actions made at this visit will be documented in a final close-out report and in a follow-up letter.

10.5. Protocol Deviations

The Investigator is not allowed to deviate from the CIP without prior approval by the Sponsor.

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 EC. These deviations will be reported to the Sponsor and to the EC, if required.

Protocol Deviations must be documented on the appropriate Protocol Deviation CRF. If a CRA becomes aware that an Investigator is not complying with the signed Investigator's Agreement, the CIP, the requirements of EN ISO 14155 or other applicable regulations, or any conditions of approval imposed by the reviewing EC, the Sponsor or Designee will

immediately either secure compliance or discontinue shipments of the investigational device to the Investigator and terminate the Investigator's participation in the investigation. The Investigator will be required to return all investigational components of the study device and system, unless this action would jeopardize the rights, safety or welfare of a patient.

Protocol deviations will be analyzed by the Sponsor for the impact to the overall integrity of the study. Disqualification is warranted when an Investigator has repeatedly or deliberately violated governing regulations or has repeatedly or deliberately submitted false information in any report. Where protocol deviations occur, which do not warrant disqualification from a study, the Sponsor or it's Designee will implement appropriate corrective and preventive actions, including repeat training as deemed necessary.

10.6. Insurance

In order to cover possible damage to health, in relation to participation in this study, the Sponsor, has, as required by law, obtained appropriate insurance coverage.

10.7. Confidentiality

In accordance with GCP and with the national data protection laws, all information concerning the subjects in the study must be treated as strictly confidential by all persons involved in the study. Health data will be recorded and forwarded to the Sponsor or its Designee, participating EC and Competent Authorities, for evaluation as required. Data processing will be performed in compliance with the EU General Data Protection Regulation (GDPR) 2016/679, and all applicable national laws..
Any information that is obtained in connection with this study that can be identified with the subjects will remain confidential. Any data that may be published in scientific journals will not reveal the identity of the study participants.

The investigator acknowledges that any and all information acquired from the Sponsor or its Designee or developed or acquired in connection with the study are strictly confidential. The investigator will not disclose any confidential information to any third party nor use confidential information for any purpose without first obtaining the consent of Sponsor in writing. Such consent shall be deemed to have been given for disclosure to any person for whom the investigator is responsible at his/her center, but only so far as required for the purposes of the study, and, in the case of disclosures to staff, only if such staff are bound by obligations of confidentiality no less strict than those set out herein.

10.8. Record Keeping and Retention

Data generated for the study should be stored in a limited-access file area and be accessible only to Designees of the study site, the Sponsor and its Designees and relevant health authorities/regulatory agencies. All reports and communications relating to study subjects will identify subjects only by subject identification number and will be pseudonymized. Complete subject identification will be kept by the investigator. This information will be treated with strict adherence to professional standards of confidentiality.

All study-related records must be maintained for at least 15 years after study completion. The Sponsor will notify the Investigator when records are no longer needed. The Investigator will

not discard any records without notifying the Sponsor. If the Investigator moves from the current investigational site, the Sponsor should be notified of the name of the person who will assume responsibility for maintenance of the records at the investigational site or the new address at which the records will be stored. The Investigator will notify the Sponsor as soon as possible in the event of accidental loss or destruction of any study documentation.

10.9. Study Final Report

The Sponsor shall provide the CA/EC and the Investigator with an accurate final report within 12 months after completion of the study, and within of 3 month in case of premature termination or discontinuation of the study. The final report may not precede final data submission which has not been monitored.

10.10. Publication

The results of the study may be submitted for publication. Upon the prior written consent of Sponsor, Investigator shall have the rights to publish papers related to the Study.

If written permission from the Sponsor is provided, the PI may publish and/or present the results of the Study conducted at their site, provided that, prior to any such publication or presentation, the site and/or the PI shall furnish the Sponsor with two (2) hard copies and one electronic copy of any materials intended for publication or presentation at least sixty (60) days prior to the submission of manuscripts. The Sponsor shall then have sixty (60) days from the receipt of such materials to review and provide the site and/or the PI with written comments.

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