

AF Septal Pacing Clinical Investigation Plan

Version 3.0 22-Nov-2017

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Clinical Investigation Plan

| | |
|-------------------------|--|
| Study Title | AF Septal Pacing |
| Study Product | Pulmonary vein ablation system |
| Sponsor | Medtronic Bakken Research Center B.V. Endepolsdomein 5 6229 GW Maastricht The Netherlands Phone: +31-43-35-66-566 Complete sponsor's study team will be provided under separate cover. |
| Document Version | 3.0 22-Nov-2017 |

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1. Investigator Statement

| | |
|----------------------------|---|
| Study title | AF Septal Pacing |
| Sponsor | Medtronic Bakken Research Center B.V. Endepolsdomein 5 6229 GW Maastricht The Netherlands |
| Version Number/Date | 3.0, 22-Nov-2017 |

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I agree to comply with Declaration of Helsinki, Clinical Investigation Plan and national local laws, regulation, standards and requirements. I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation and conduct of the clinical investigation without the prior written consent of Medtronic.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Medtronic. I will discuss this material with them to ensure that they are fully informed about the products and the study.

| | |
|----------------------------------|--|
| Investigator's Signature: | |
| Investigator's Name: | |
| Institution: | |
| Date: | |

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2. Glossary

| Term | Definition |
|------|---|
| ADE | <i>Adverse Device Effect</i> |
| AE | <i>Adverse Event</i> |
| AF | <i>Atrial Fibrillation</i> |
| AFCL | <i>Atrial Fibrillation Cycle Length</i> |
| ATP | <i>Anti-tachycardia Pacing</i> |
| BP | <i>Blood Pressure</i> |
| CE | <i>Conformity European</i> |
| CIP | <i>Clinical Investigation Plan</i> |
| CRF | <i>Case Report Form</i> |
| CS | <i>Coronary Sinus</i> |
| CTA | <i>Clinical Trial Agreement</i> |
| CV | <i>Curriculum Vitae</i> |
| DD | <i>Device Deficiency</i> |
| DTL | <i>Delegated Task List</i> |
| EC | <i>Ethic Committee</i> |
| ECG | <i>Electrocardiogram</i> |
| EP | <i>Electrophysiology Procedure</i> |
| ICF | <i>Informed Consent Form</i> |
| ISF | <i>Investigator Site File</i> |
| LA | <i>Left Atrium</i> |

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| <i>Term</i> | <i>Definition</i> |
|--------------------|--|
| <i>PCL</i> | <i>Pacing Cycle Length</i> |
| <i>PV</i> | <i>Pulmonary Vein</i> |
| <i>RA</i> | <i>Right Atrium</i> |
| <i>SADE</i> | <i>Serious Adverse Device Effect</i> |
| <i>SAE</i> | <i>Serious Adverse Event</i> |
| <i>USADE</i> | <i>Unanticipated Serious Adverse Device Effect</i> |

3. Synopsis

| Title | AF Septal pacing | | | |
|---|--|-------------------|---|--|
| Clinical Study Type | Non-randomized, non-controlled, acute, single-arm research study | | | |
| Product Name | PV ablation system | | | |
| Sponsor | Medtronic Bakken Research Center B.V. Endepolsdomein 5 6229 GW Maastricht The Netherlands | | | |
| Indication under investigation | Subjects suffering of either persistent and paroxysmal Atrial Fibrillation, indicated for ablation of the pulmonary vein. | | | |
| Investigation Purpose | To evaluate the feasibility to obtain a stable position of a ring of stimulation electrodes on the interatrial septum. | | | |
| Product Status | All devices used in this clinical study are CE marked and used within the approved indications in the participating countries. The devices and accessory components that might be used in the study are listed in the below table 1: | | | |
| Table 1: Devices and accessory components used in AF Septal Pacing | | | | |
| Component and Model name | Comments | Regulatory Status | Intended Use | Investigational |
| Decapolar Lasso catheter (Biosense Webster, model number Lasso 2515 NAV) | Preferably the Lasso Biosense Webster catheter, since it was used in acute animal studies and positive results were obtained. Positive results were not obtained with the PVAC and MASC catheter. | CE marked | Indicated for multiple electrode electrophysiological mapping of the cardiac structures of the heart, i.e. recording or stimulation only. The catheter is designed to obtain electrograms in the atrial regions of the heart. | NO (CE marked used within approved indications) |

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| | | | (one per subject) | |
| Achieve catheter (Medtronic Inc) (single use) (model 990063-020) | In case no stable position can be obtained with the Lasso catheter, we will use the Achieve catheter from Medtronic. | CE marked | Indicated as an intra-cardiac electrophysiology (EP) recording catheter and can be used for cardiac stimulation during electrophysiology studies. (one per subject) | NO (CE marked used within approved indications) |
| EP4 stimulator (St Jude, Minneapolis, USA, model number H403023) | Or any other four channel electrophysiological stimulator standard used in the EP lab of the hospital. | CE marked | Indicated as a cardiac stimulator. (one per site) | NO (CE marked used within approved indications) |
| Monitoring catheters: two decapolar mapping electrodes | Any decapolar routinely used in the hospital to monitor signals in right atrium and coronary sinus. | CE marked | Monitoring (one per subject) | NO (CE marked used within approved indications) |
| Monitoring system. | Could be e.g. a stationary Bard EP recording system, a physiological recorder, such as the porti-system (TMSI) or any other electrophysiological monitoring system used in EP lab | CE marked | Monitoring (one per site) | NO (CE marked used within approved indications) |

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| | | | | | |
|---|--|--------------------------------|--|--|--|
| | | during the ablation procedure. | | | |
| Primary Objective | To evaluate the feasibility to obtain a stable position of a ring of stimulation electrodes on the interatrial septum. | | | | |
| Secondary Objectives | <ul style="list-style-type: none">• Localized Atrial Capture: evaluate if during the rapid pacing phase of the dual-stage septal pacing scheme (rapid pacing followed by a step-wise transition to slow-pacing) from multiple electrodes on the interatrial septum, local atrial capture can be observed during atrial fibrillation.• AF Termination Scheme: evaluate if AF termination can be obtained using a dual-stage septal pacing scheme (rapid pacing followed by a step-wise transition to slow-pacing) from multiple electrodes on the interatrial septum. | | | | |
| Study Design | Approximately 15 subjects with AF indicated for ablation of the pulmonary vein will be enrolled in the study. Participants will attend the Baseline visit and the Procedure visit. The baseline visit can be on the same day as the ablation procedure. Since it is an acute study, no follow-up visit will occur. The research procedure will be performed during an already scheduled ablation procedure. Subjects will be enrolled over a period of approximately 18 months | | | | |
| Sample Size | Approximately 15 subjects suffering of either persistent and paroxysmal Atrial Fibrillation, indicated for ablation of the pulmonary vein will be enrolled in the study. No control group will be used for this study. The study is planned to be conducted at up to 3 centers in Europe. | | | | |
| Inclusion/Exclusion Criteria | <p>All of below inclusion criteria must be met:</p> <ul style="list-style-type: none">• Patient referred to the center to undergo ablation of the pulmonary vein using radiofrequency (initial AF ablation, or redo procedure).• In case of paroxysmal, AF the right atrium should be dilated as indicated by $> 29 \text{ ml mm}^2$ or the left atrium should be dilated as indicated by $> 34 \text{ ml mm}^2$.• Patient is willing and able to cooperate with the study procedure.• Patient is willing to provide the Informed Consent for their participation in the study. <p>None of the below exclusion criteria must be met:</p> <ul style="list-style-type: none">• Patients under 18 years or over 80 years old.• Women who are currently pregnant or have a positive pregnancy test.• Patients with an implantable cardiac device.• Patients who already underwent an AF septal ablation procedure. | | | | |
| Study Procedures and Assessments | <p>Baseline: Patients will be pre-screened for potential enrolment in the clinical investigation by evaluating if the patients meet the inclusion and exclusion criteria. Next the patient is asked for her or his informed consent. A patient is considered an enrolled subject after he/she has personally signed and dated the ICF. At baseline, subject characteristics will be noted such as age, gender, weight, height, AF status and AF history.</p> | | | | |

Enrolled subjects will undergo the AF ablation procedure, for which they have been referred to the center. For this standard procedure, the subject will be prepared as per standard catheterization/EP procedures, which includes administration of anesthesia/analgesia, ECG and BP monitoring.

Procedure:

The subject will be sedated. A trans-septal puncture will be made to access the left atrium and place a septal catheter and the clinically used ablation catheter. One decapolar recording catheter will be placed in the right atrium and one decapolar recording catheter will be placed in the coronary sinus. Both decapolar catheters are used according to standard clinical practice. The standard procedure workflow is visualized on the left side of figure 1 below.

After successful pulmonary vein isolation, there is a routine waiting time of half an hour to confirm efficacy of the ablation procedure. During this waiting period, the study procedure will be performed. The deviations from the standard procedure are indicated in orange on the right of figure 1 below. The septal catheter, already in place in the right atrium, will be positioned on the left interatrial septum via a trans-septal approach. In most cases the patient will be in sinus rhythm.

During sinus rhythm pacing thresholds and impedances on all septal catheter electrodes will be determined. Also, potential ventricular capture will be assessed.

Next, atrial fibrillation will be induced by rapid atrial pacing. AF cycle length will be determined, during 1 minute of atrial fibrillation using the ablation catheter electrodes. Subsequently, the rapid phase of the two-stage atrial pacing scheme will be applied to four septal electrodes at same time during half a minute using the quadripolar electrophysiological stimulator (e.g. EP4 stimulator). An electrophysiological recording system (already in place for the AF ablation procedure), recording all atrial electrograms, will be used to assess the study outcome of local atrial capture. In addition, if feasible, AF termination will be evaluated using the two-stage pacing algorithm. If needed cardioversion will be used to terminate AF.

In a minority of cases the subject will still be in AF after successful pulmonary vein isolation. In these cases, the ventricular capture tests as described above will be performed first, then AF cycle length will be determined, and the rapid phase of the two-stage atrial pacing scheme as described above will be performed. If delivery of the two-stage atrial pacing scheme either will not be feasible or not stop the AF, the subject will be externally cardioverted under deep sedation as would have been done as common practice at the end of the ablation procedure. Next, during sinus rhythm pacing thresholds and impedances on all septal catheter electrodes will be determined.

Protocol deviations from what is stated above will be documented.

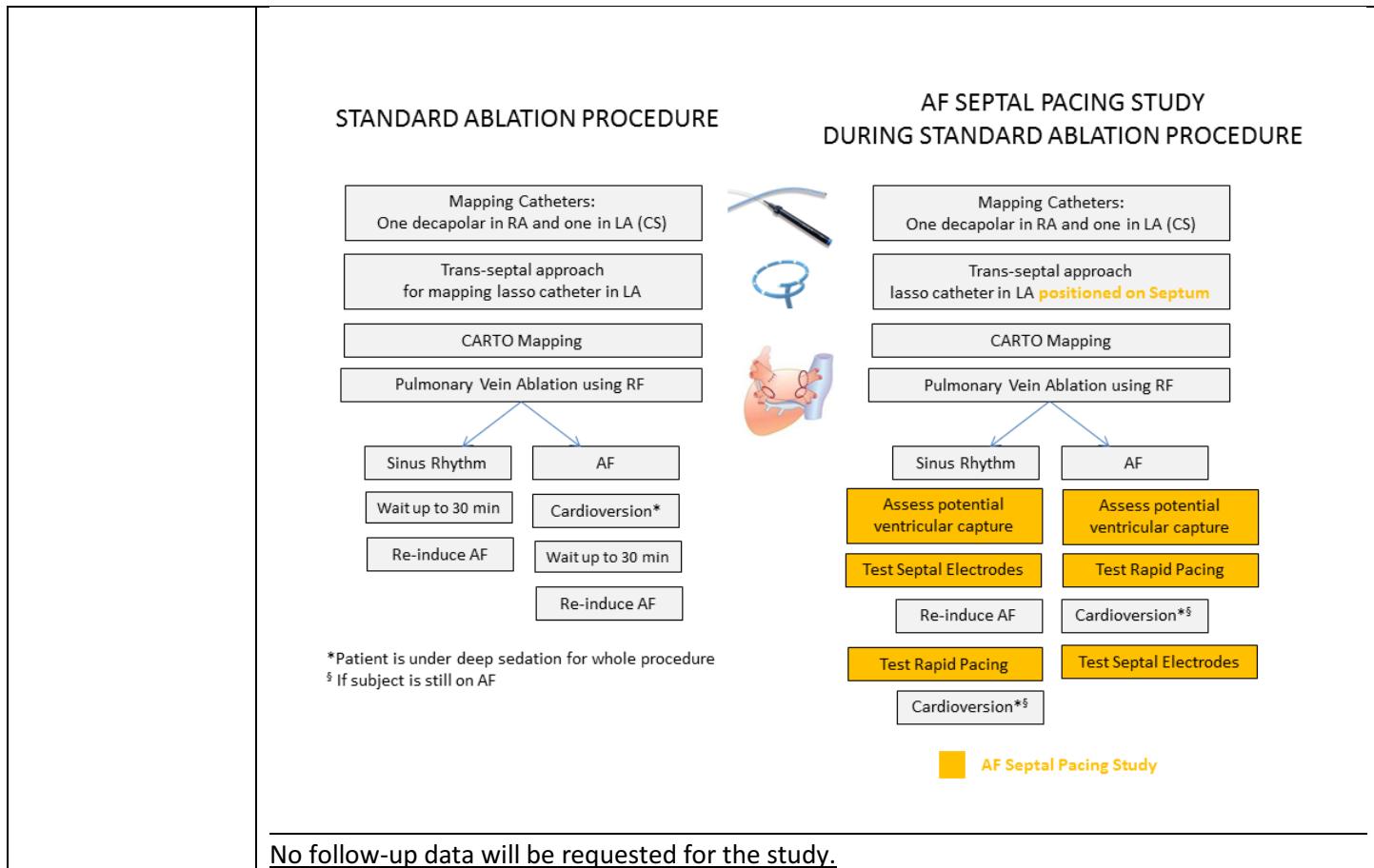
Figure 1: Study steps to be added to standard procedure.

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4. Introduction

4.1. Background

Pacemaker-based therapy for atrial fibrillation (AF) has been discussed as an alternative to drugs and ablation for patients with a conventional indication for pacing.^{1,2} Today, many pacemakers and implantable defibrillators include pacing algorithms developed for the prevention or the termination of AF.¹ Most existing pacing algorithms have a preventive nature, designed to suppress AF triggers and to reduce the dispersion of atrial refractoriness that predisposes to re-entry.² Preventive pacing algorithms are primarily designed to decrease premature atrial contractions and prevent pauses, but results of clinical trials with these algorithms have been mixed, probably because of the differences in study design, pacing algorithms and patient populations.³⁻⁶ Anti-tachycardia pacing (ATP) algorithms designed to terminate atrial tachycardia's deliver pacing bursts at a cycle length shorter than that of the detected arrhythmia.^{1,2} While successful ATP could be

observed in terminating atrial flutter or organized atrial tachycardia's, it has proved difficult to interpret the results from clinical studies evaluating ATP for AF.^{1,7,8} Therefore, the evidence of treating AF by pacing is limited, although these algorithms are of interest, since they appear to be safe and usually add little additional cost.^{3,6}

One reason why clinical studies are often non-conclusive, could be that they focus on AF frequency and burden, but few of them are aimed at evaluating the effect of AF pacing on the atrial tissue.⁹ More detail can be found in animal and human mapping experiments: although termination of AF by rapid pacing was not observed, the possibility of creating an area of local capture of the atrial tissue by rapid pacing of AF has been demonstrated.¹⁰⁻¹⁴ To overcome the limitations of human and animal experiments, a computer model of AF has been used to systematically simulate all existing ATP algorithms on AF and test all pacing locations.¹⁵ This systematic model-based testing of site rapid pacing of AF revealed that the septum was the only pacing site that yielded sporadic AF capture episodes in both atria, but this in general did not result in AF termination or permanent changes in AF patterns. Based on this result, a new dual-stage septal pacing has been developed in the computer model: rapid pacing was applied from the septal area following a dual-stage scheme: 1) rapid pacing for 10-30 s at pacing intervals 62-70% of AF cycle length (AFCL), 2) slow pacing for 1.5 s at 180% AFCL, initiated by a single stimulus at 130% AFCL.¹⁶ The proposed septal pacing algorithm could suppress AF reentries in a more robust way than classical single site rapid pacing and at an optimal pacing cycle length (64% AFCL) up to 29% of AF termination was observed in the computer model¹⁶. Septal pacing of AF is therefore proposed here as a simple and attractive approach since it may produce simultaneous bi-atrial stimulation using a single lead, without the need of complex methods for synchronizing multiple pacing sites.

The feasibility of pacing both atria simultaneously from a single lead placed in the interatrial septum has been previously demonstrated clinically¹⁷. These results motivated the testing of atrial septal pacing both as a way to prevent AF occurrence, or to terminate ongoing AF. Clinical studies evaluating the preventive effect of atrial septal pacing have led to mixed results. Becker et al. showed in a canine model that septal pacing produced comparable results as quadruple site pacing in terms of prevention of paroxysmal AF and activation times¹⁸. Kale et al. showed that atrial septal pacing in combination with antiarrhythmic drugs resulted in a subjective improvement of symptoms in patients with drug-refractory paroxysmal AF¹⁹. On the other hand, Hermida et al. showed that atrial septal pacing did not prevent the occurrence of AF²⁰. Hakacova et al. found no significant difference between septal and high atrial preventive pacing, using AF duration and the number of AF episodes as endpoints²¹. A multicenter prospective randomized study by Padeletti et al. showed that preventive pacing of atrial tachycardia's from the septum was associated with a decreased frequency of symptomatic episodes and premature atrial contractions.⁵ In all these studies, safety of interatrial septal pacing was demonstrated. Interest in septal pacing still persists, as is seen in a multicenter parallel randomized study on 380 patients with paroxysmal AF, currently being conducted to evaluate whether septal pacing with or without atrial overdrive pacing could have an effect on AF suppression²².

The AF septal pacing algorithm concept, which is a dual-stage septal pacing scheme (rapid pacing followed by a step-wise transition to slow-pacing) from a ring of stimulation electrodes on the interatrial septum, is described in Figure 2 and in the publication by Uldry et al¹⁶. The septal pacing concept had been developed and tested in a computer model of AF and

in a pig model²³. Experimental studies are now needed to determine whether similar termination mechanisms and efficacies can be observed in humans.

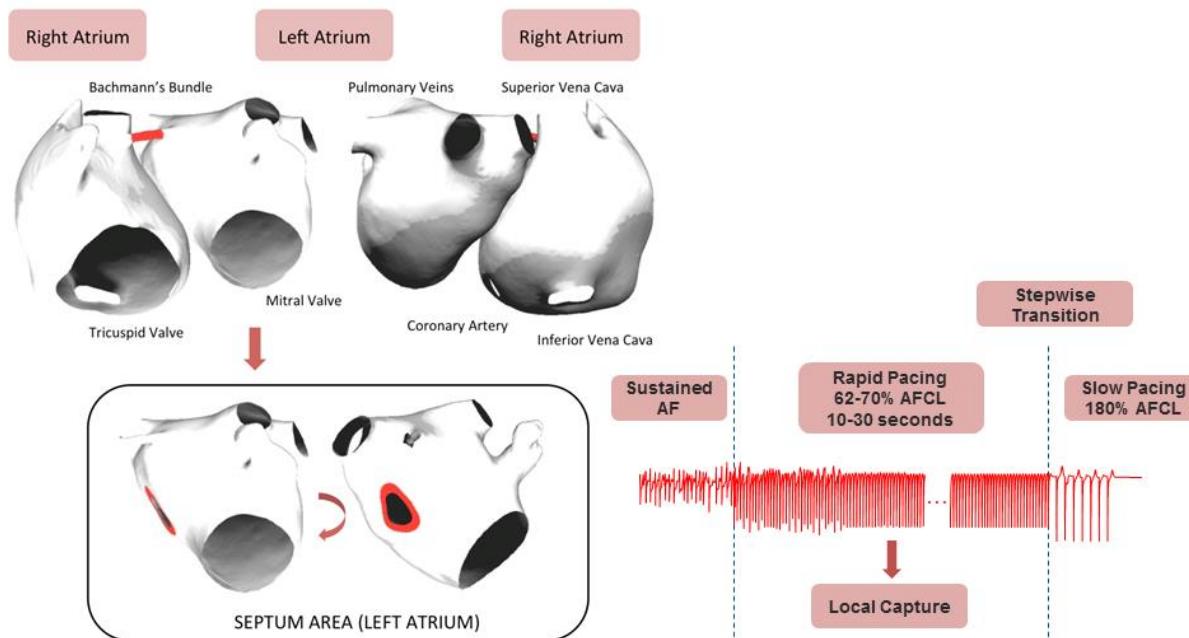


Figure 2: Septal-pacing dual-stage pacing scheme: rapid pacing until local capture is achieved, followed by slow pacing, with a step-wise transitions from 130% AFCL (one cycle) to 180% AFCL. Electrodes on the septum should be placed in the area indicated in red (as found in the computer model Luca et al²⁴).

4.2. Purpose

The purpose of this non-randomized, non-controlled, acute, single-arm research study is to evaluate the feasibility to obtain a stable position of a ring of stimulation electrodes on the interatrial septum.

5. Objectives and Endpoints

5.1. Objectives

5.1.1. Primary Objective

The primary objective of the study is to evaluate the feasibility to obtain a stable position of a ring of stimulation electrodes on the interatrial septum.

5.1.2. Secondary Objectives

The secondary objectives of this study are:

- Localized Atrial Capture: evaluate if during the rapid pacing phase of the two-stage septal pacing scheme (rapid pacing followed by a step-wise transition to slow-pacing) from multiple electrodes on the interatrial septum, local atrial capture can be observed during atrial fibrillation.
- AF Termination Scheme: evaluate if AF termination can be obtained using a dual-stage septal pacing scheme (rapid pacing followed by a step-wise transition to slow-pacing) from multiple electrodes on the interatrial septum.

5.2. Endpoints

5.2.1. Primary Endpoint

To assess Pacing Site Stability, the number of interatrial septal pacing electrodes which are successfully placed in a stable position, will be counted. A stable position in this study is defined as a location where the pacing threshold will be < 10 mA at a pacing pulse width of 1 msec. Stable pacing further requires that no ventricular capture will be induced during atrial stimulation at twice the atrial capture threshold.

5.2.2. Secondary Endpoint(s)

To assess Localized Atrial Capture the following endpoints will be considered:

- The number of AF episodes in which local capture is recorded during atrial septal stimulation in at least one of the electrode positions
- The number of electrodes for which local capture is determined using pacing schemes with various pacing cycle lengths (PCL) for a duration of 10-30 seconds depending on when capture occurs, at the start of the scheme followed, if feasible, by slow pacing for 1.5 s at 180% AFCL, initiated by a single stimulus at 130% AFCL.
- The spatial extend of capture (assessed from the atrial electrograms recorded from the multipolar right atrial catheter and the multipolar coronary sinus catheter) to obtain local atrial capture obtained with septal pacing of AF, will be assessed off-line after the study procedure.

To assess whether AF termination can be obtained using a dual-stage septal pacing scheme, the surface ECG will be analyzed and the PCL and stimulation current used will be noted to measure the number of subjects in which the pacing scheme successfully terminates the AF episode.

6. Study Design

The AF Septal Pacing study is a non-randomized, non-controlled, acute, single-arm research study that will be conducted in up to three European centers.

Approximately 15 subjects with AF indicated for ablation of the pulmonary vein will be enrolled in the study. Participants will attend the Baseline visit and the Procedure visit. The baseline visit can be on the same day as the ablation procedure. Since it is an acute study, no follow-up visit will occur. The research procedure will be performed during an already scheduled ablation procedure. Subjects will be enrolled over a period of approximately 18 months.

The point of enrollment is the time when subject signs and dates the Informed Consent Form (ICF). At that point, the subject is considered included in the study.

Selection of subjects, treatment of subjects, and evaluation of study data are potential sources of bias. Methods incorporated in the study design to minimize potential bias include (but are not limited to):

- Patients will be screened to confirm eligibility for enrollment in accordance to the inclusion/exclusion criteria.
- Subject demographics will be collected at baseline on possible differences that may affect the primary objective.
- All study clinicians, participating site personnel, and Medtronic personnel will be trained on their respective pertinent role of the study using standardized training materials.

No control group, no randomization and no blinding will be used in this Study.

6.1. Duration

The expected total study duration is approximately 18 months accordingly to the forecasted enrollment period. Participants will attend the Baseline visit and the Procedure visit (can be on the same day). The results of the study are expected to be ready for internal review approximately 3 months after the last subject visit is completed.

6.2. Rationale

Available literature does not provide a conclusive message on the effect of septal pacing in preventing AF recurrences or suppression of AF. A specific algorithm of pacing the interatrial septal area using a multipolar electrode ring on the intra-atrial septal wall has been designed, with the aim to terminate AF episodes. Following the positive results obtained on a computer model of AF, studies in humans are warranted to obtain information on the feasibility of this pacing strategy.

7. Product Description

7.1. General

All devices used in this clinical study are CE marked and used within the approved indications in the participating countries. The devices will be used to evaluate the feasibility to obtain a stable position of a ring of stimulation electrodes on the interatrial septum. The devices and accessory components that might be used in the study are listed in the below table 1:

Table 1: Devices and accessory components used in AF Septal Pacing

| Component and Model name | Comments | Regulatory Status | Intended Use | Investigational |
|---|--|-------------------|--|--|
| Decapolar Lasso catheter (Biosense Webster, model number Lasso 2515 NAV) | Preferably the Lasso Biosense Webster catheter, since it was used in acute animal studies and positive results were obtained ²³ . Positive results were not obtained with the PVAC and MASC catheter. | CE marked | Indicated for multiple electrode electrophysiological mapping of the cardiac structures of the heart, i.e. recording or stimulation only. The catheter is designed to obtain electrograms in the atrial regions of the heart. (one per subject) | NO (CE marked used within approved indications) |
| Achieve catheter (Medtronic Inc) (single use) (model 990063-020) | In case no stable position can be obtained with the Lasso catheter, we will use the Achieve catheter from Medtronic. | CE marked | Indicated as an intra-cardiac electrophysiology (EP) recording catheter and can be used for cardiac stimulation during electrophysiology studies. (one per subject) | NO (CE marked used within approved indications) |
| EP4 stimulator (St Jude, Minneapolis, USA, model | Or any other four channel electrophysiological stimulator standard | CE marked | Indicated as a cardiac stimulator. (one per site) | NO |

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| Component and Model name | Comments | Regulatory Status | Intended Use | Investigational |
|--|--|-------------------|------------------------------|---|
| number H403023) | used in the EP lab of the hospital. | | | (CE marked used within approved indications) |
| Monitoring catheters: two decapolar mapping electrodes | Any decapolar routinely used in the hospital to monitor signals in right atrium and coronary sinus. | CE marked | Monitoring (one per subject) | NO (CE marked used within approved indications) |
| Monitoring system. | Could be e.g. a stationary Bard EP recording system, a physiological recorder, such as the porti-system (TMSI) or any other electrophysiological monitoring system used in EP lab during the ablation procedure. | CE marked | Monitoring (one per site) | NO (CE marked used within approved indications) |

Pacing system: A clinical electrophysiological stimulator will be used to deliver the dual stage septal pacing protocol to pace and potentially terminate atrial fibrillation. The stimulator should offer four independent pacing channels, to be able to independently stimulate the four electrodes of the interatrial septal catheter. If no four-channel electrophysiological stimulator is available at the clinical study site, study site can request Medtronic reimburse a commercially available four channel electrophysiological stimulator (St. Jude Medical – EP4-Stimulator). The provided stimulator is to be used in accordance with this Clinical Investigation Plan and for this study only.

Pacing catheters: A multipolar (decapolar) Lasso catheters will be used to pace the interatrial septum. In acute animal studies, a Biosense-Webster Lasso Catheter was successfully used²³. Therefore, it is preferable to use the Lasso catheter in this study unless experiences in this human study support the use of another Lasso catheter such as the Achieve. The decapolar Lasso or Achieve catheter will be used according to standard clinical practice.

Monitoring Catheters: Standard electrophysiological recording according to standard clinical practice during AF ablation will be used. This includes the use of a decapolar coronary sinus (CS) electrophysiological recording catheter, and the use of a decapolar right atrial (RA) electrophysiological recording catheter.

Monitoring System: Atrial electrocardiograms will be recorded throughout the study procedure. Intra-atrial electrocardiograms will be recorded from the right atrial decapolar catheter, the coronary sinus catheter and the interatrial septal catheter. All signals will be recorded on the available electrophysiological recording system.

The products needed are already available at the site as standard material used for the routine clinical ablation procedure, for which the patient is indicated and referred to the site.

As a first choice the decapolar Lasso catheter (Biosense Webster, Diamond Bar, USA) will be used. In case this catheter is not effective in the patient, the Achieve catheter (Medtronic) will be used. In case these catheters are not standardly used during the ablation procedure, Medtronic will provide the catheter(s) in accordance with section 7.4.

7.2. Manufacturer of devices

- Decapolar Lasso catheter (Biosense Webster Inc, Diamond Bar, CA, USA)
- Achieve catheter, Medtronic, Inc., 710 Medtronic Parkway, Minneapolis, MN 55432-5604, USA
- EP4 Stimulator (St Jude Medical, St Paul, MN, USA)

7.3. Intended Population

A sample size of approximately 15 subjects with either persistent and paroxysmal Atrial Fibrillation indicated for the ablation of the pulmonary vein will be enrolled to test if the developed pacing algorithm can terminate AF episodes.

7.4. Equipment

Only in case the participating site didn't have the devices listed in section 7.1 already in its electrophysiological department, the required devices may be provided to the participating study sites by the sponsor upon written request by study site.

In such cases the sponsor, only after site activation and submission of the relative invoice request including supporting documentation, will re-fund the costs related to the purchase of the devices listed in section 7.2 linked to enrolled subjects. Relating to the enrolled study subjects in case the Achieve produced by Medtronic is not used as a standard of care and is needed for the study it will be provided by Medtronic. In case the Lasso produced by Biosense Webster is not used as a standard of care and is needed for the study it will be reimbursed by Medtronic.

In case of need technical support, maintenance and calibration of the study-specific equipment after site delivery will be done by manufacturer representative as per standard agreement between manufacturers and site administration.

Since all devices used during this study are CE marked and used within the approved indication all devices will be labeled in local language, according to local regulation.

7.5. Product Use

For a description of each important component, ingredient, property and principle of operation of the device system/product, including any materials in contact with tissues or body fluids, refer to the relative device Manual.

7.6. Product Training Requirements

Prior to investigation site activation or subsequent involvement in clinical study activities, Medtronic will provide clinical study training relevant and pertinent to the involvement of personnel conducting clinical study activities. As a minimum, investigator responsibilities, Declaration of Helsinki, Clinical Investigation Plan (CIP), ICF, use of data collection tools and applicable local regulations. Study-specific training will be documented prior to investigation site activation or for additional site team members after site activation, prior to them conducting any study-specific tasks.

7.7. Product Storage

Any equipment provided to the site by Medtronic will be stored in a secure location at the site until the end of the procedure of the last enrolled patient.

7.8. Product Return

If applicable at the end of the study the multi-use equipment (EP4 stimulator) provided to the site will be collected by Medtronic personnel and returned to the sponsor.

In case of provision to the site if any of the single use device (Lasso or Achieve catheter) will not be used it will be returned to Medtronic.

7.9. Product Accountability

Each component provided to the site will be traced during the clinical study recording on a specific device tracking log, with the relative serial numbers, with date of receipt, use and final return date to Medtronic. The investigator is responsible for maintenance of each Device Tracking Log (DTL) in the Investigator Site File (ISF). On this log, the receipt,

return and use of the study devices shall be documented. At the end of the clinical study the principal investigator must sign and date the original Device Tracking Logs.

The site will also receive the following study material for the proper conduction to the study:

- Investigator Site File (ISF) to be updated during the study course
- Patient binders

8. Selection of Subjects

8.1. Study Population

Approximately 15 subjects suffering of either persistent and paroxysmal Atrial Fibrillation, indicated for ablation of the pulmonary vein will be enrolled in the study. No control group will be used for this study. The study is planned to be conducted at up to 3 centers in Europe.

In case of missing data of enrolled subject would significantly affect the possibility to properly address study objectives the subject will be replaced in order to have at least 15 complete analyzable subjects' datasets to analyze atrial septal pacing lead stability.

8.2. Subject Enrollment

A subject is considered enrolled in this clinical study at the time at which he/she signed and dated the ICF. The investigator will maintain a log of all subjects enrolled in the clinical investigation, assigning an identification code linked to their names, alternative subject identification or contact information.

8.3. Inclusion Criteria

All of below inclusion criteria must be met:

- Patient referred to the center to undergo ablation of the pulmonary vein using radiofrequency (initial AF ablation or redo procedure).
- In case of paroxysmal AF, the right atrium should be dilated as indicated by $> 29 \text{ ml mm}^2$ or the left atrium should be dilated as indicated by $> 34 \text{ ml mm}^2$.
- Patient is willing and able to cooperate with the study procedure.
- Patient is willing to provide the Informed Consent for their participation in the study.

8.4. Exclusion Criteria

None of the below exclusion criteria must be met:

- Patients under 18 years or over 80 years old.
- Women who are currently pregnant or have a positive pregnancy test.
- Patients with an implantable cardiac device
- Patients who already underwent an AF septal ablation procedure.

9. Study preparation

9.1. Investigator/Investigation site selection

An investigator/investigation site may be included in the investigation if the investigator/investigation site complies with the following requirements:

- Investigator/site is qualified by training, education, and relevant experience appropriate to the use of the product and associated procedures
- Investigator/site expects to have adequate time and resources to conduct the study throughout the duration of the study
- Investigator/site has access to an adequate number of eligible subjects
- Ability to comply with applicable Ethics Committee (EC) and regulatory requirements (if applicable)
- Investigator is not debarred, disqualified, or working under sanctions in the applicable region

At time of study protocol definition no investigator/investigation site have been already selected, so the complete list of participating investigators/investigation sites, including their details, will be provided under a separate cover once investigator/investigation site selection will be completed.

9.2. Site activation

Before performing study related activities, all requirements shall be fulfilled, including, but not limited to the following:

- EC approval (and voting list, as required by local law) of the current version of the CIP and ICF.
- Regulatory Authority approval or notification (as required per local law)
- Fully executed Clinical Trial Agreement (CTA)
- Curriculum Vitae (CV) of investigators and key members of the investigation site team

- Documentation of delegated tasks
- Documentation of study training.

Additional requirements imposed by the EC and Regulatory Authority shall be followed, as appropriate.

Medtronic may distribute pre-populated study-specific ISF and will provide site with documentation of study site/investigator readiness. Evidence of site/investigator readiness must be received prior to subject enrollment and must be filed in the ISF.

10. Study Procedures

Baseline:

Patients will be pre-screened for potential enrolment in the clinical investigation by evaluating if the patients meet the inclusion and exclusion criteria. Next the patient is asked for her or his informed consent. A patient is considered an enrolled subject after he/she has personally signed and dated the ICF. At baseline, subject characteristics will be noted such as age, gender, weight, height, AF status and AF history.

Enrolled subjects will undergo the AF ablation procedure, for which they have been referred to the center. For this standard procedure, the subject will be prepared as per standard catheterization/EP procedures, which includes administration of anesthesia/analgesia, ECG and BP monitoring.

Procedure:

The subject will be sedated. A trans-septal puncture will be made to access the left atrium and place a septal catheter and the clinically used ablation catheter. One decapolar recording catheter will be placed in the right atrium and one decapolar recording catheter will be placed in the coronary sinus. Both decapolar catheters are used according to standard clinical practice. The standard procedure workflow is visualized on the left side of figure 1 below.

After successful pulmonary vein isolation, there is a routine waiting time of half an hour to confirm efficacy of the ablation procedure. During this waiting period, the study procedure will be performed. The deviations from the standard procedure are indicated in orange on the right of figure 1 below. The septal catheter, already in place in the right atrium, will be positioned on the left interatrial septum via a trans-septal approach. In most cases the patient will be in sinus rhythm. In these cases, during sinus rhythm pacing thresholds and impedances on all septal catheter electrodes will be determined. Also, potential ventricular capture will be assessed. Next, atrial fibrillation will be induced by rapid atrial pacing. AF cycle length will be determined, during 1 minute of atrial fibrillation using the ablation catheter electrodes. Subsequently, the rapid pacing phase of the two-stage atrial pacing scheme will be applied to four septal electrodes at same time during half a minute using the quadripolar electrophysiological stimulator (e.g. EP4 stimulator). An electrophysiological recording system (already in place for the AF ablation procedure), recording all atrial electrograms, will be used to assess the study

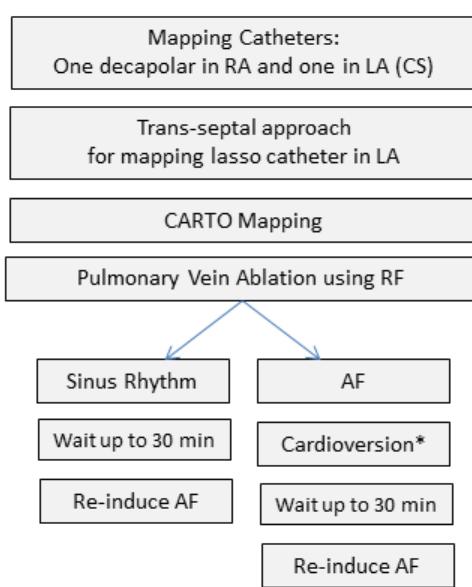
outcome of local atrial capture. In addition, if feasible, AF termination will be evaluated using the two-stage pacing algorithm. If needed cardioversion will be used to terminate AF.

In a minority of cases the subject will still be in AF after successful pulmonary vein isolation. In these cases, the ventricular capture tests as described above will be performed first, then AF cycle length will be determined, and the two-stage atrial pacing scheme as described above will be performed. If delivery of the slow pacing phase of the two-stage atrial pacing scheme either will not be feasible or not stop the AF, the subject will be externally cardioverted under deep sedation as would have been done as common practice at the end of the ablation procedure. Next, during sinus rhythm pacing thresholds and impedances on all septal catheter electrodes will be determined.

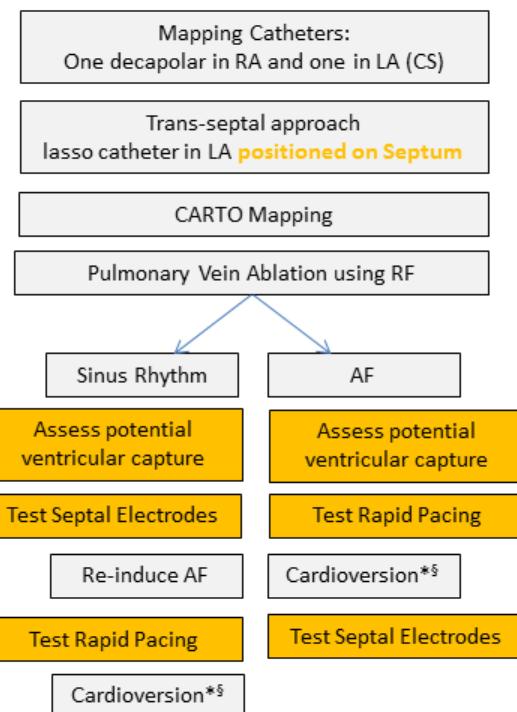
Protocol deviations from what is stated above will be documented.

Figure 1: Study steps to be added to standard procedure.

STANDARD ABLATION PROCEDURE



AF SEPTAL PACING STUDY DURING STANDARD ABLATION PROCEDURE



*Patient is under deep sedation for whole procedure
§ If subject is still on AF

No follow-up data will be requested for the study.

Sponsor's representatives may provide support as required for the clinical study, including:

- Provide study training relevant and pertinent to the involvement of personnel conducting study activities and investigator responsibilities;
- Technical support during AF Septal Pacing procedure.

- Technical support at all visits under the supervision of a study investigator, but no data entry, shall be performed by Medtronic personnel or their representatives at sites;
- Provide clarification in case of need on correct completion and/or correction of CRFs;
- Monitoring and auditing activities;

The sponsor's representatives providing technical support during AF Septal Pacing procedure will be listed on the sponsor's technical support list.

10.1. Schedule of Events

The point of enrollment is the time when a subject signs the ICF. At that point, the subject is considered included in the study.

Approximately 15 subjects indicated for pulmonary vein ablation will be enrolled in the study. Participants will be invited to attend the Baseline and Procedure visit. The baseline visit can be on the same day as the ablation procedure.

After signing the ICF, the subject will be prepared for the ablation procedure for which he/she was indicated. After the ablation procedure and before the testing of efficacy of this procedure, the study procedure will be performed. The expected duration of the study procedure is approximately 30 minutes. The study procedure will take place during the routine waiting period following the ablation procedure. Since this is an acute study no follow up is expected and a Study Exit form will be completed after the research procedure.

Subjects will be enrolled over a period of approximately 18 months. The results of the study are expected to be ready for internal review approximately 3 months after the last subject visit is completed.

Table 2 – Data collection

| Data Criteria | Baseline | Procedure | Exit |
|------------------------------|----------|-----------|------|
| Informed Consent | ✓ | | |
| Inclusion/Exclusion Criteria | ✓ | | |
| Demographics | ✓ | | |
| ECG | ✓ | | |
| BP | ✓ | | |
| Devices information | | ✓ | |

| | | | |
|---|--|---|---|
| Study procedure parameters (Impedance, Pacing threshold, Ventricular capture, safety test, PCL, mA) | | ✓ | |
| Exit / withdrawal CRF | | | ✓ |
| Adverse Events and Device Deficiencies | As they occur, assessed throughout the study | | |
| Deviations | | | |

10.2. Subject Consent

The investigator or authorized designee must obtain written informed consent before any clinical study related activity takes place.

Legally incompetent subjects will not be included in this study.

Well in advance of the consent discussion, the subject should receive the Medtronic and EC approved Subject Information and ICF. During the consent discussion, the investigator or his/her authorized designee must fully inform the subject of all aspects of the clinical study that are relevant to the subject's decision to participate in the clinical study. Patient is willing and able to sign the Informed Consent and to cooperate with study procedure. All items addressed in the Patient Information and the ICF must be explained. The language used shall be as non-technical as possible and must be understandable to the subject and the impartial witness, where applicable.

The subject must have ample time and opportunity to read and understand the Subject Information and the ICF, to inquire about details of the clinical study, and to decide whether or not to participate in the clinical study. All questions about the clinical study should be answered to the satisfaction of the subject.

Neither the investigator, nor the investigation site staff shall coerce or unduly influence a subject to participate or to continue to participate in the clinical study. The informed consent process shall not waive or appear to waive the subject's rights.

The sponsor will revise the written Subject Information and ICF whenever new information becomes available during the course of the study which are pertinent to the safety and well-being of the subject, as this could impact a subject's willingness to participate in the study. The revised information will be sent to the investigator for approval by the EC. After approval by the EC, a copy of this information must be provided to the new participating subjects. If relevant, approval may be requested from subjects already enrolled and exited to the study to inform them.

When the subject decides to participate in the clinical study, the ICF must be signed and personally dated by the subject and investigator or authorized designee. If applicable, the witness shall also sign and personally date the consent form to attest that the information in the Patient Information and ICF was accurately explained and clearly understood by the subject, and that informed consent was freely given.

After all persons have signed and dated the ICF, the investigator must provide the subject with a copy of the Subject Information and the signed and dated ICF.

The study specific Master ICF will be provided under a separate cover.

10.3. Assessment of Efficacy

During sinus rhythm, the number of cases in which the septal pacing electrodes are successfully placed in a stable position will be registered. A stable position is defined as a location where the atrial septal pacing threshold is lower than 10 mA at 1msec on all electrodes and where no ventricular capture at twice the atrial capture threshold is observed.

When the subject is in sinus rhythm after PV ablation, as a first step the atrial pacing threshold is determined, for each electrode, using a pulse width of 1 msec. Also, the impedance is determined for each electrode. During atrial stimulation at high threshold currents, ventricular capture may be possible and absence of ventricular capture at the atrial capture threshold measurement will be confirmed by stimulating from each electrode with twice the atrial capture threshold current (corresponding to specific electrode) from all electrodes at the same time using overdrive pacing at 20 bpm. If ventricular capture is observed during atrial stimulation at twice the atrial capture threshold, the position of the catheter on the septum will be changed and the tests for measuring thresholds, impedances and ventricular capture will be repeated until no ventricular capture occurs during atrial pacing at twice the atrial capture threshold. If it does not occur we will increase the current up to 20 mA and repeat sequence mentioned above. The maximum current will be that current, which does not induce ventricular capture when stimulating from all four electrodes at same time and is 20 mA or lower.

Next, atrial fibrillation will be induced by rapid atrial pacing, gradually elevating the atrial pacing rate until 1:1 atrial capture is lost. AF cycle length will be determined by recording the atrial electrogram on the septum. Stimulation on the septum from all electrodes starts at the current defined above, using various pacing cycle length (PCL), being percentages of AFCL and will last for 10 to 30 seconds, depending on when capture occurs, followed, if feasible, by slow pacing using an interval of 130% of AF for one cycle followed by 1.5 second of 180% of AF Cycle length at maximum output which did not induce ventricular capture (20 mA or lower). Multiple PCLs will be used to start the pacing sequence. During each stimulation sequence, corresponding to each PCL, atrial capture at each recording electrode will be assessed. The optimal parameters for stimulation will be used to determine local capture for all electrodes.

When the subject will still be in AF after successful pulmonary vein isolation the ventricular capture tests will be performed first during atrial fibrillation (as described above for subject in sinus rhythm). Then, AF cycle length will be determined and

the two-stage atrial pacing scheme as described above will be performed. If delivery of the two-stage atrial pacing scheme either will not be feasible or not stop the AF, the subject will be externally cardioverted under deep sedation as would have been done as common practice at the end of the ablation procedure. Next, during sinus rhythm pacing thresholds and impedances on all septal catheter electrodes will be determined.

To assess if the two-stage pacing scheme can terminate AF, the surface ECG will be analyzed and PCL and stimulation current will be noted.

10.4. Assessment of Safety

All Adverse Event (AE) as defined in Section 11 will be collected and reported as described in the same section.

10.5. Recording Data

Clinical data will be collected at baseline and during the ablation visit. After completion of the ablation visit, the subject's participation in the study is considered complete and a Study Exit form should be completed. Data will be collected via paper Case Report Forms (CRFs) and episodes, which will be stored on the electrophysiological recording system. The investigator is responsible for the preparation (review and signature) of the CRF. The investigator will allow inspections of the study site and documentation by study personnel and audit personnel from Medtronic or designee, EC, external auditors, or representatives of regulatory authorities. The purpose of these inspections is to verify and corroborate the data collected on the CRFs. In order to do this, direct access to medical or clinical records is necessary.

The investigator must ensure accuracy, completeness and timeliness of the data reported in the CRFs and in all other required reports. Data reported on the CRFs which are derived from source documents, such as patient medical records, must be consistent with the source documents or the discrepancies need to be justified in a documented rationale, signed and dated by the (principal) investigator, to be filed in the subject file. All baseline and medical history data must be derived from source documents. Only authorized persons can complete CRFs. Sponsor study personnel will review all collected data and create data queries for missing data that impacts data analysis or inconsistencies. Queries will be sent to the investigator or appropriate support staff for resolution.

The following data will be collected as summarized in Table 2 – Data collection:

- Demographic data for subjects, Relevant medical history (including arrhythmia history), Medications, Subject demographics, Physical Examination, Inclusion/exclusion assessment;
- Procedure Data: electrophysiological recording system data, EGM, ECG PCL, capture threshold current, Capture occurrence, Impedance, Pacing threshold, Ventricular capture occurs at (20 bpm overdrive pacing).

The investigator should mark clinical records to indicate that the subject is enrolled in this clinical investigation and to document subject consent process. Subject's medical record will be used as source documents. Worksheets could serve as source documentation in particular cases if a data field is not in the subject's medical record.

In order to maintain an audit trail, changes or corrections in CRFs are made by making a single strike-through on the wrong data and an addition of the correct data. The change in the CRF must be signed, dated, and explained (if necessary) by the person that made the change. If a person only authorized to complete CRFs made changes to an already signed CRF, the investigator shall re-sign this CRF.

Sponsor study personnel will review all CRF and create data queries for missing data that impacts data analysis. Queries will be sent to the investigator or appropriate support staff for resolution.

Where copies of the original source document as well as print outs of original electronic source documents are retained, these shall be signed and dated by a member of the investigation site team with a statement that it is a true reproduction of the original source document.

It is expected that CRFs will be completed within one month from the performed visit or as soon as source documents are available, except for AE which must be reported as defined in the relative section.

All device data recorded by the monitoring system of the hospital will be stored as electronic files on SD cards or USB flash drives or directly on the hard disk drive of the personal computer provided by sponsor and will be delivered via a secure web-based application (as BOX) or via mail in a timely manner.

A delayed completion of the e-CRF will not be considered a Protocol Deviation.

10.6. Deviation Handling

A protocol deviation is an event where the investigator or investigation site personnel did not conduct the clinical study according to the CIP or CTA. The investigator is not allowed to deviate from the above mentioned documents except with prior approval and under emergency circumstances. All deviations shall be documented and explained, regardless the reason for the deviation.

At the minimum, the following items will be considered as Protocol Deviations:

- Subject Informed Consent process not performed in the correct way (e.g. wrong ICF version used);
- Inclusion/Exclusion criteria violation;
- Not performed Protocol Required Data Collection/Testing

All the Protocol Deviations will be reviewed and classified by the clinical study team and appropriate actions will be determined, including any associated EC and regulatory reporting requirements, if applicable. The clinical study team will review a comprehensive summary of deviations at least on a quarterly basis to decide if measures must be taken to avoid recurrence of deviations.

Medtronic will assess the significance of all deviations and evaluate the need to amend the CIP or to early terminate the investigation, in accordance with Medtronic SOPs.

The investigator shall obtain documented approval from Medtronic, before implementation, for any change in- or deviation from the CIP. In case of study deviations that can affect the subject's rights, safety and well-being or the scientific integrity of the clinical study, approval from the EC and regulatory authority must also be obtained before implementation. The investigator shall timely contact the Clinical Study Manager for review of the proposed change/deviation.

Prior approval is not always realistic in situations where unforeseen circumstances are beyond the investigator's control. However, also in these cases, the event is considered a deviation, and shall be reported.

In any emergency situation the investigator shall exercise his/her judgment to safeguard the subject's interest. Such deviations from the CIP do not require the prior approval of Medtronic. The investigator shall report the deviation as soon as possible to Medtronic and the reviewing EC, if applicable. Medtronic will inform the regulatory authorities, if required.

All the Protocol Deviations will be documented in the appropriate CRFs.

The investigator shall adhere to EC requirements and procedures for reporting study deviations.

Medtronic is responsible for analyzing deviations, assessing their significance, and identifying any additional corrective and/or preventive actions (e.g. amend the CIP, additional training, terminate the study, etc.). Repetitive or serious investigator compliance issues may result in the need to initiate a corrective action plan, and in some cases freeze enrolment or ultimately terminate the investigator's participation in the clinical study. Medtronic will provide investigation site-specific reports to the investigators on a periodic basis summarizing information on deviations that occurred at the investigation site.

10.7. Subject Withdrawal or Discontinuation

If a subject is withdrawn from the clinical study, the reason for withdrawal shall be recorded in the study exit form and in the subject's hospital record. If discontinuation is because of safety the subject shall be asked to be followed for collecting safety data outside the clinical study.

Possible reasons for withdrawn from the study are:

- Subject withdrew consent;

- Investigator withdrew subject from the study for medical reasons;
- Investigator withdrew subject from the study due to inclusion/exclusion criteria not met.

Subjects withdrawn might be replaced in case the number of dropouts will significantly affect the possibility to properly address study objectives.

Since AF septal pacing will only be used to collect data only for the time of the clinical study, there is no specific medical care that will be provided to the subjects after the clinical study will be completed or in case of subject withdrawal.

11. Risks and Benefits

11.1. Potential Risks

The AF septal pacing system consists of commercially available devices routinely used for PV ablation within their intended use.

Anticipated Adverse Event and Adverse Device Effect due to planned PV ablation are listed in the respective device manuals (including their likely incidence and relative methods of mitigation).

The study specific procedure risks are reduced as much as possible and disclosed in the ICF provided to subjects. During the course of the study, risks will be continuously monitored, assessed and documented by the investigators.

The potential risk, mitigations and risk controls associated with the AF septal pacing research procedure are summarized in Table 3.

Table 3 - Potential study specific procedure risk and risk minimization

| Potential AF septal pacing risk | Minimization |
|---------------------------------------|--|
| Induction of a ventricular arrhythmia | <ul style="list-style-type: none">• Applying a ventricular capture test at the stimulation output of our tests. In case of any paced QRS complex, the voltage will be lowered or the lead will be repositioned.• Stimulation will be induced at a level not able to induce ventricular capture.• The patient's rate and rhythm will be monitored during the procedure.• Patch electrodes will be attached to the patient to be able to deliver a shock in case of an emergency during the procedure |

11.2. Potential Benefits

There is no immediate individual benefit for a patient participating in this study. The information gained from this study could result in the improved management of patients with AF, which could benefit future patients.

11.3. Risk-Benefit Rationale

It is expected that the potential risks associated with the conduct of this trial are minimal using safety measures to prevent induction of ventricular arrhythmia and since:

1. All the devices used in the study are CE-Marked and used within their intended use.
2. Standard of care will be followed by the sites for the ablation procedure.

12. Adverse Events and Device Deficiencies

12.1. Definitions/Classifications

For the purposes of the clinical report, Medtronic will classify each Adverse Event according to ISO 14155:2011.

Where the definition indicates "device", it refers to any device used in the study. This might be the device under investigation, or any market released component of the system.

Adverse Event (AE): (ISO14155:2011 3.2)

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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.

NOTE 1: This definition includes events related to the investigational medical device or the comparator.

NOTE 2: This definition includes events related to the procedures involved.

NOTE 3: For users or other persons, this definition is restricted to events related to investigational medical devices.

Adverse Device Effect (ADE): *(ISO14155:2011 3.1)*

Adverse event related to the use of an investigational medical device.

NOTE 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

NOTE 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device

Serious Adverse Event (SAE): *(ISO 14155:2011 3.37)*

Adverse event that

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

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

Serious Adverse Device Effect (SADE): *(ISO 14155:2011 3.36)*

Adverse device effect that has resulted in any of the consequences characteristic of a Serious Adverse Event.

Unanticipated Serious Adverse Device Effect (USADE): *(ISO 14155:2011 3.42)*

Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report

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.

Device deficiency: *(ISO 14155:2011 3.15)*

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.

12.2. Reporting of Adverse Events

Recording and reporting of Adverse Events

In this study all the Adverse Event (AE) information will be collected and reported to Medtronic on an Adverse Event Form, one for each Adverse Event.

All Adverse Events, regardless of relatedness or outcome, must be reported.

The principal investigator shall:

- a) Record every adverse event and observed device deficiency, together with an assessment;
- b) Report to the sponsor, without unjustified delay, all serious adverse events and device deficiencies that could have led to a serious adverse device effect; this information shall be promptly followed by detailed written reports, as specified in the CIP;
- c) Report to the EC serious adverse events and device deficiencies that could have led to a serious adverse device effect, if required by the national regulations or CIP or by the EC;
- d) Report to sponsor serious adverse events and device deficiencies that could have led to a serious adverse device effect, as required by the national regulations, and
- e) Supply the sponsor, upon sponsor's request, with any additional information related to the safety reporting of a particular event.

See the Adverse Event CRF for the information to be reported for each Adverse Event.

For Adverse Events that require immediate reporting (see Table 4), initial reporting may be done by e-mail, or on the CRF completing as much information as is available. The completed Adverse Event CRF must be sent to Medtronic as soon as possible.

In case an adverse event, which is related to procedure or device is not completed at the time of the subject exit, the subject shall be asked to be followed by the physician for collecting safety data outside the clinical study.

In case the Adverse Event is related to a non-Medtronic market released device used during the study, post market surveillance is also applicable and the investigator is responsible for immediate reporting of the product complaint via the regular channels for market released products.

In case the investigator requires information from the sponsor in an emergency situation, the investigator can contact rs.mstsafetycrdm@medtronic.com.

Recording and reporting of Device Deficiencies

Device Deficiency (DD) information will be collected throughout the study and reported to Medtronic. Device Deficiencies that did not lead to an Adverse Event should be reported on a Device Deficiency Form, one for each Device Deficiency. This Device Deficiency form must be filled in the CRF and immediately sent to Medtronic contact (see below).

See the Device Deficiency CRF for the information to be reported for each Device Deficiency that did not lead to an Adverse Event.

Device deficiencies that did not lead to an Adverse Event but could have led to an SADE

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

require immediate reporting (see Table 4). Initial reporting may be done by e-mail (see below for contact details), or on the CRF completing as much information as is available. The completed Device Deficiency CRF must be sent to Medtronic as soon as possible.

Adverse Event and Device Deficiency review process

All Adverse Events and Device Deficiencies will be reviewed by Medtronic Safety Specialist. This review will include the determination whether the Adverse Event/Device Deficiency meets regulatory reporting requirements (see Table 4). The sponsor will ensure timely Adverse Event/Device Deficiency reporting to meet global regulatory requirements.

A list of anticipated or foreseeable adverse events that are expected to be related to AF septal pacing procedures is included in the table 3.

In case the Adverse Event/Device Deficiency is related to a Medtronic market released device used during the study, the Medtronic Safety Specialist will immediately report this device related Adverse Event/Device Deficiency to the Medtronic responsible Complaint Handling Unit. The responsible Complaint Handling Unit will ensure prompt review, and appropriate reporting.

Table 4: Adverse Event reporting requirements

| Serious Adverse Device Effects (SADE), including Unanticipated Serious Adverse Device Effect (USADE): | |
|--|---|
| Investigator submit to: | |
| Medtronic | Immediately* after the investigator first learns of the event or of new information in relation with an already reported event. |
| Regulatory Authority | As per local reporting requirement |
| EC | Reporting timeframe as per local EC requirement. |
| Sponsor submit to: | |
| Regulatory Authorities | Reporting timeframe as per local requirement. |
| EC | Submit to EC per local reporting requirement. |
| Serious Adverse Events (SAE) | |
| Investigator submit to: | |
| Medtronic | Immediately* after the investigator first learns of the event or of new information in relation with an already reported event. |
| Regulatory Authority | As per local reporting requirement |
| EC | Submit to EC per local reporting requirement. |
| Sponsor submit to: | |
| Regulatory Authorities | Reporting timeframe as per local requirement. |
| EC | Submit to EC per local reporting requirement. |
| Adverse Device Effects (ADE) | |
| Investigator submit to: | |
| Medtronic | Immediately* after the investigator first learns of the event. |
| Regulatory Authority | As per local reporting requirement |
| EC | Submit to EC per local reporting requirement. |
| Sponsor submit to: | |
| Regulatory Authorities | Reporting timeframe as per local requirement |

| | |
|--|---|
| EC | Submit to EC per local reporting requirement. |
| All other AEs | |
| Investigator submit to: | |
| Medtronic | Submit in a timely manner** after the investigator first learns of the event. |
| Regulatory Authority | As per local reporting requirement |
| EC | Submit to EC per local reporting requirement. |
| Device Deficiency with SADE potential | |
| Investigator submit to: | |
| Medtronic | Immediately* after the investigator first learns of the deficiency or of new information in relation with an already reported deficiency. |
| Regulatory Authority | As per local reporting requirement |
| EC | Submit to EC per local reporting requirement. |
| Sponsor submit to: | |
| Regulatory Authorities | Reporting timeframe as per local requirement |
| EC | Submit to EC per local reporting requirement. |
| All other Device Deficiencies | |
| Investigator submit to: | |
| Medtronic | Submit in a timely manner** after the investigator first learns of the deficiency. |
| Regulatory Authority | As per local reporting requirement |
| EC | Submit to EC per local reporting requirement. |

* Per MEDDEV 1.7/3 maximum within 3 calendar days after site study personnel's awareness of event.

**Within 3 calendar days after site study personnel's awareness of event.

Emergency contact details in case of serious AEs

In case of an immediately reportable Adverse Event the investigators can contact rs.mtsafetycrdm@medtronic.com.

13. Data Review Committees

This feasibility study will not involve any Data Monitoring Committee, Steering Committee, Safety Committee or Adverse Event Advisory Committee as no clinical/therapeutic intervention is being applied or evaluated.

14. Statistical Design and Methods

14.1. Sample Size

As this is a feasibility study, no formal statistical hypotheses are being tested and no sample size calculation was performed.

14.2. Patients sets considered for the analysis

The analysis set will include all enrolled patients matching inclusion/exclusion criteria (Intention to Treat).

14.3. Primary endpoints

See 5.2

14.4. Secondary endpoints

See 5.2

14.5. Interim analysis

No interim analysis is planned. Data will be analyzed once the last enrolled patient completes all planned study procedures.

14.6. Handling of missing data

Since the impact of missing data is expected to be small no multiple imputation method for missing data is planned.

14.7. Subgroup Analysis

No pre-specified subgroup analyses are planned.

14.8. Deviation from the original statistical plan

Any deviation(s) from the original statistical plan will be described and justified in the final report.

15. Ethics

15.1. Statement(s) of Compliance

This clinical study will be conducted in compliance with the Declaration of Helsinki (2013), laws and regulations of the country in which the clinical study is conducted, including data protection laws, the CTA and the CIP.

Prior to first enrollment at a study center or any study procedures at that study center, approval of the CIP and additional deliverables required needs to be obtained from the study center's country specific regulatory authorities and an EC, as applicable.

EC approval of the clinical study must be received in the form of a letter and provided to Medtronic before commencement of the clinical study at an investigation site. The approval letter must contain enough information to identify the version or date of the documents approved. If this information is not contained in the approval letter, it must be retrievable from the corresponding submission letter. In addition, the approval letter needs to be accompanied by an EC roster or letter of compliance, to allow verification that the investigator, other investigation site personnel, and/or Medtronic personnel are not members of the EC. If they are members of the EC, written documentation is required stating that he/she did not participate in the approval process. Investigators must inform Medtronic of any change in status of EC approval once the investigation site has started enrollment. If any action is taken by an EC with respect to the investigation, that information will be immediately forwarded to Medtronic by the respective investigator.

Any additional requirements imposed by the EC or regulatory authority shall be followed, if appropriate.

Medtronic Bakken Research Center B.V. is a wholly owned subsidiary of Medtronic plc., which as the parent company of such entity maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a study insurance statement/certificate will be provided to the EC and the competent authority.

The subjects enrolled will not receive any compensation for the participation in the study. They will only receive compensation for reasonable, necessary and properly documented (e.g., copy of train ticket) travel expenses in connection with participation in the study.

All principles of the Declaration of Helsinki have been implemented in this clinical study by means of the informed consent process, EC approval, study training, clinical study registration on www.ClinicalTrial.gov public database and study result posting, preclinical testing, risk benefit assessment, publication policy, etc.

Prior to investigation site activation or subsequent involvement in clinical study activities, Medtronic will provide clinical study training relevant and pertinent to the involvement of personnel conducting clinical study activities.

As a minimum, investigator responsibilities, Declaration of Helsinki, the CIP, ICF, use of data collection tools, applicable local regulations are required. Study-specific training will be documented prior to investigation site activation.

16. Study Administration

16.1. Monitoring

It is the responsibility of Medtronic to ensure proper monitoring of the study per regulations. Appropriately trained Medtronic personnel or delegates appointed by Medtronic will perform study monitoring at the study center in order to ensure that the study is conducted in accordance with the CIP, the CTA, and applicable regulatory requirements. Medtronic must therefore be allowed direct access to the subject's clinic and hospital records when so requested as per the ICF and CTA.

Monitoring visits could be conducted at the start, during and at the closure of the clinical study in accordance with Medtronic SOPs and the Monitoring Plan. Frequency of monitoring visits will occur based on subject enrollment, study compliance, findings from previous monitoring visits and any suspected inconsistency in data that requires investigation.

The monitoring activities will include at least verification of signed and dated ICFs have been correctly obtained from each subject and that all required study documents are filed into the ISF. Source data verification will be performed as defined in the Monitoring Plan.

16.2. Data Management

The information collected by paper CRFs and reported to Medtronic will be stored in a secure location at the site. The investigator must ensure accuracy, completeness and timeliness of the data reported in the CRFs.

Only authorized persons can complete and sign CRFs, as specified on the Delegated Task list (DTL) included in the ISF.

16.3. Direct Access to Source Data/Documents

The principal investigator(s), his/her delegate(s) and the study coordinator(s) shall be accessible to Medtronic field personnel and the Clinical Study Manager/Scientist. This accessibility is of particular importance for reviewing data in the CRF. Direct access to subject medical files for source data verification will need to be granted and prepared prior to any monitoring visits.

Medtronic may conduct audits at participating investigation sites. The purpose of an audit is to verify the adequate performance of the study related activities. Independent of the employees involved in the study. Regulatory authorities

may also perform inspections at participating investigation sites. Any regulatory authority inspection announcements shall be forwarded immediately to the Study Manager.

The investigator and/or institution shall permit Medtronic and regulatory bodies direct access to source data and documents, taking into account any restrictions due to local law, to perform study-related monitoring, audits, EC review and regulatory inspections.

16.4. Confidentiality

All records and other information about subjects participating in this study will be treated as confidential. The identity of a subject will never be disclosed in the event that study data are published.

Subject confidentiality will be maintained throughout the clinical study in a way that ensures the information can always be tracked back to the source data. For this purpose, a unique subject identification code will be assigned and used to allow identification of all data reported for each subject.

Study data may be made available to third parties, e.g. in the case of an audit performed by regulatory authorities, provided the data are treated confidentially and that the subject's privacy is guaranteed. Sites will maintain subject privacy according to local and national regulations and institutional requirements.

16.5. Liability

No subject compensation is forecasted.

16.6. CIP Amendments

If the investigator will propose any appropriate modification(s) of the CIP or investigational device/product or investigational device/product use Medtronic will review this proposal and decide whether the modification(s) will be implemented.

Medtronic will submit any significant amendment to the CIP, including a justification for this amendment, to the appropriate regulatory authorities if applicable and to the investigators to obtain approval from their EC. The investigator will only implement the amendment after approval of the EC, regulatory authority and sponsor. Administrative amendments to the CIP will be submitted to the EC for notification or approval in case the EC policy requires administrative amendments to be approved as well. Furthermore CIP amendment will be executed after investigators signature collection for any approved amendment for agreement.

16.7. Record Retention

The investigator is responsible for the preparation and retention of the records cited below. All of the below records, with the exception of case report forms and source documents, should be kept in the ISF (i.e., the study binder provided to the investigator) or Subject Study Binder. CRFs must be maintained and signed at the site. At a minimum, the following records must be kept by the investigator for a period of two years (or longer as local law or hospital administration requires) after the date on which the investigation is terminated:

- Signed and dated ICF
- Documentation of the dates and rationale for any deviation from the protocol
- Signed and dated CRFs (including AEs, DDs and CRF corrections)
- Subject ID log
- All approved versions of the CIP, ICF
- Signed CTA
- Current signed and dated CV of principal investigators and members of investigation site team included in the delegated task list.
- Documentation of delegated tasks
- Technical Support List
- EC approval documentation. Written information that the investigator or other study staff, when member of the EC, did not participate in the approval process. Approval documentation must include the EC composition
- Study training records for site staff
- Insurance certificates, if required
- List of investigation sites
- Correspondence related to the study
- Name and contact information of monitor(s)
- Reports of AEs and DDs
- Regulatory authority notification, correspondence and approval if applicable
- Accountability logs of sponsor provided devices (if applicable)
- Final Study Report

A copy of the Final Clinical Study Report will be provided by the Investigator to the EC.

Medtronic shall maintain the following accurate, complete, and current records:

- Internal tracking of Medtronic provided devices (if applicable)
- Signed CTA
- Current signed and dated CV of principal investigator and members of the investigation site team included in the delegated task list
- Delegated Task List
- Technical Support List
- All approved ICF versions
- Copies of all EC approval letters and relevant EC correspondence and EC voting list/roster/letter of assurance
- Names of the institutions in which the clinical study will be conducted
- Insurance certificates, if applicable
- Final report of the clinical study
- The approved CIP and any revision
- Study training records for site personnel and Medtronic personnel involved in the study
- Correspondence related to the study
- Name and contact information of monitor(s)
- Statistical Analysis
- Regulatory authority notification, correspondence and approval if applicable
- Monitoring visit reports and relative follow-up letters
- Other study reports
- Signed and dated CRFs, including AE and DD forms, and CRF corrections

After closure of the study, all records and reports will be archived indefinitely.

16.8. Publication and Use of Information

Publications and presentations referring to this clinical study will be coordinated by Medtronic to allow the use of all available data. The following publication policy will have to be adhered to by all participating investigation sites:

Medtronic may intend to publish the results of the study in scientific journals and congresses.

There are no plans to form a publication committee. Publication activities will be assessed after the study is completed and any collaboration with the investigator will be determined at that time.

Authorship on any publication(s) resulting from this clinical study will be assigned according to substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data, drafting the article or revising it critically for important intellectual content, final approval of the version to be published and agreement to be accountable for all aspects of the work in ensuring that all questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This is in accordance with the Vancouver principles (The Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication, Latest ICMJE

Recommendations ("Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals", 2013), as agreed upon by the editors of all major medical journals.

The number of authors will be dependent on the regulations of the concerning journal.

Based on the principle that Medtronic owns the data of this clinical study, a single investigation site not access and use the data provided by itself for scientific publications unless there is prior approval by Medtronic.

Medtronic as the owner of the data can use the data and/or any results derived from the data or publications based on that data for marketing purposes, further research and development of devices or educational use or submission to Regulatory Authority.

The study sponsor will collect data in such way that no subject can be identified, and monitor study records.

Participating subjects will not be identified by name in any published reports about the clinical study.

16.9. Suspension or Early Termination

Medtronic or Regulatory Authority (if applicable) may decide to suspend or prematurely terminate the clinical study (e.g. if information becomes available that the risk to study subject is higher than initially indicated). If the clinical study is terminated prematurely or suspended, Medtronic shall promptly inform the investigators of the termination or suspension and the reason(s) for this. The investigator shall then promptly inform the reviewing EC and the study subjects and their personal physician.

Medtronic, EC or Regulatory Authority (if applicable) may decide to suspend or prematurely terminate an investigation site (e.g. in case of expiring approval of the reviewing EC, non-compliance to the CIP or lack of enrollment). If an investigation site is suspended or prematurely terminated, Medtronic shall promptly inform the investigator(s) of the termination or suspension and the reason(s) for this. The investigator shall then promptly inform the reviewing EC and the study subjects and their personal physician.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definite outcomes, investigators must assess whether to continue, modify or immediately stop the clinical study in the respective investigation site and immediately inform the sponsor and EC, if applicable.

In case of early investigation site suspension or termination subjects will be followed-up as per standard of care.

In case of early investigation site suspension or termination the investigator must notify site suspension or termination to EC and Regulatory Authority, if required.

In case of close out, the investigators will be notified and notification/report to Medtronic, EC and Regulatory Authority will be done, if required.

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18. Version History

| Version | Summary of Changes | Author(s)/Title |
|---------|---|---|
| 1.0 | Not Applicable, New Document | Silvia Giuli, Clinical Research Manager |
| 2.0 | <p>Section 3 and 10:</p> <ul style="list-style-type: none">Research procedures order changed for subjects in atrial fibrillation after pulmonary vein ablation, first assess potential ventricular capture, then test rapid pacing, next apply cardioversion if needed and finally test pacing characteristics septal electrodes.Figure 1 updated according to new order research procedures. <p>Section 10.3:</p> <ul style="list-style-type: none">Research procedures order changed for subjects in atrial fibrillation after pulmonary vein ablation, first assess potential ventricular capture, then test rapid pacing, next apply cardioversion if needed and finally test pacing characteristics septal electrodes.Added specification to AF cycle length “at maximum output which did not induce ventricular capture (20 mA or lower)” | Silvia Giuli, Clinical Research Manager |
| 3.0 | <p>Section 5.1.2</p> <ul style="list-style-type: none">Added “rapid pacing phase” to “the two-stage pacing scheme” <p>Section 5.2.2</p> <ul style="list-style-type: none">“Three different PCL” replaced with “various PCL”Added “if feasible” related to the possibility to perform the slow pacing phase of the two-stage pacing scheme <p>Section 7.1</p> <ul style="list-style-type: none">Added word “potentially” related to the AF termination <p>Section 10</p> | Elisa Scaccianoce, Clinical Study Manager |

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| | <ul style="list-style-type: none">Deleted “in the left atrial appendage”Added “rapid pacing phase” to “the two-stage pacing scheme”“at least a minute” replaced by “half a minute”Added “if feasible” related to the possibility to perform the slow pacing phase of the two-stage pacing scheme and to terminate AF <p>Section 10.1</p> <ul style="list-style-type: none">Aggregated Adverse Events and Device Deficiencies forms <p>Section 10.3</p> <ul style="list-style-type: none">“an optimal” PCL replaced by “various PCLs, being percentage of AFCL”“Three different PCL” replaced with “multiple PCL” | |
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