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Sustained Treatment of Paroxysmal Atrial Fibrillation Post-Approval Study
(STOP AF PAS)

Clinical Investigation Plan

18 AUG 2011

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Table of Contents

Sustained Treatment of Paroxysmal Atrial Fibrillation Post-Approval Study 1
(STOP AF PAS) 1
Clinical Investigation Plan 1
18 AUG 2011 1
List of Appendices 4
List of Tables 4
Table of Figures 4
CONTACT INFORMATION 5
1 INTRODUCTION 6
1.1 Study Purpose 6
1.2 Study Scope 6
2 BACKGROUND AND JUSTIFICATION 6
3 SYSTEM DESCRIPTION AND INTENDED USE 6
3.1 Product Used in the Study 6
4 METHODOLOGY 7
4.1 Study Design 7
4.2 Primary Effectiveness Objective 9
4.3 Primary Safety Objective 9
4.4 Secondary Objectives 10
4.5 Site Selection 11
4.6 Subject Selection 12
4.7 Minimization of Bias 15
5 STUDY PROCEDURES 16
5.1 Equipment requirements 16
5.2 Informed Consent Process 16
5.3 Data Collection Overview 18
5.4 Subject Follow-Up Schedule 19
5.5 Baseline 19
5.6 Cryoablation Procedure 20
5.7 Scheduled Follow-up Visits 21
5.8 Unscheduled Follow-up Visits 23
5.9 Termination Follow-up Visits 23
5.10 Visit Procedure Details 24
5.11 Recurrence of Atrial Fibrillation 26
5.12 Permissible Retreatment of Study Subjects 26
5.13 Study Exit 26
5.14 Lost to Follow-Up 27
5.15 Subject Follow-up after Withdrawal 27
5.16 Medication Restrictions 27
6 STUDY DEVIATIONS 28
7 ADVERSE EVENTS 29
7.1 Adverse Event Assessment 29
7.2 Adverse Event Definitions, Classification and Reporting 30
7.3 Adverse Event Classification and Reporting 32
7.4 Subject Death 34

7.5 Adverse Event Adjudication Committee (AEAC) Review 35
7.6 Medical Device Reporting Requirements for User Facilities 35
7.7 Investigator Adverse Event Records and Reporting Requirements 36
7.8 Medtronic Adverse Event Records and Reporting Requirements 37
8 RISK ANALYSIS 38
8.1 Risk Minimization 38
8.2 Potential Benefits 38
9 PLANNED STUDY CLOSURE, EARLY TERMINATION OR STUDY SUSPENSION 38
9.1 Planned Study Closure 38
9.2 Early Termination or Suspension 39
9.3 Criteria 39
9.4 Procedures 40
10 STATISTICAL METHODS AND DATA ANALYSIS 41
10.1 Primary Effectiveness Endpoint 41
10.2 Primary Safety Endpoint 41
10.3 Analysis Sets 43
10.4 Sample Size Justification 43
10.5 Statistical Analysis Methods 44
10.6 Interim Patient Safety Monitoring 48
11 DATA AND QUALITY MANAGEMENT 48
12 WARRANTY/INSURANCE INFORMATION 49
12.1 Warranty 49
13 MONITORING 49
13.1 Monitoring Visits 49
14 REQUIRED RECORDS AND REPORTS 50
14.1 Investigator Records 50
14.2 Investigator Reports 51
14.3 Sponsor Records 53
14.4 Sponsor Reports 53

List of Appendices

Appendix A: Protocol Acronyms and Abbreviations 57
Appendix B: Summary of STOP AF PAS Protocol Changes 59

List of Tables

Table 1: Study Contact Information 5
Table 2: Cryoablation Procedure Event 10
Table 3: Major Atrial Fibrillation Events 11
Table 4: Data Collection/Study Procedure Requirements at Subject Visits 18
Table 5: Subject Follow-up Windows 19
Table 6: Adverse Event Definitions 30
Table 7: Adverse Event and Subject Death Classification Responsibilities 33
Table 8: Subject Death Classification Definitions 34
Table 9: Investigator Adverse Event Reports 36
Table 10: Medtronic Adverse Event reporting 37
Table 11: Cryoablation Procedure Events 42
Table 12: Major Atrial Fibrillation Events 47
Table 13: Investigator Reports for all Geographies per Medtronic requirements 51
Table 14: Investigator Reports Applicable to the United States per FDA Regulations 52
Table 15: Sponsor Reports for Canada 54
Table 16: Sponsor Reports for the United States 55
Table 17: Study Milestones/Timeline 56

Table of Figures

Figure 1: STOP AF PAS Overall Study Design 8

CONTACT INFORMATION

Medtronic contact information is provided below. This information is subject to change during the course of the clinical study. Periodic updates to study contact information will be sent to the centers.

Table 1: Study Contact Information

Study Sponsor Contacts	
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Worldwide Imaging Core Lab Name Phone Fax email	

1 INTRODUCTION

1.1 Study Purpose

The purpose of the Post-Approval Study (PAS) is to provide long-term safety and effectiveness of the Arctic Front® Cardiac Cryoablation Catheter System, including the Freezor® *MAX* Cardiac cryoablation catheter according to the Product Labeling. This PAS is a condition of the Pre-Market Approval order (P100010) by the Food and Drug Administration.

1.2 Study Scope

The study will be expected to be conducted at a minimum of 30 centers located in the United States and Canada. Up to 400 subjects will be enrolled to achieve the primary endpoint analyses. Subjects will be followed for 5 years from their cryoablation procedure date. It is expected to take 18-24 months to enroll 400 subjects. At least 70% of the total subject enrollments are required to come from the new Arctic Front user investigational sites as defined in Section 4.5 of this protocol, while the remaining subject enrollments can come from the STOP AF/CAP AF investigational sites.

2 BACKGROUND AND JUSTIFICATION

The pivotal trial of the Arctic Front® Cardiac Cryoablation Catheter System with the adjunctive use of the Freezor® *MAX* Cardiac Cryoablation Catheter to electrically isolate pulmonary veins (PV) in patients with paroxysmal atrial fibrillation (PAF), compared to a randomized drug control group demonstrated that 69.9% [62.3, 76.9% 95% CI] of experimental subjects were free of atrial fibrillation at 12 months compared to 7.3% in the control group. The proportion of experimental subjects with serious adverse events related to the cryoablation procedure was 3.1% [6.3% 95% upper confidence bound] which was well within the pre-defined 95% upper confidence bound of 14.8%.

3 SYSTEM DESCRIPTION AND INTENDED USE

3.1 Product Used in the Study

For the purpose of this study the Arctic Front® Cardiac CryoAblation System is indicated for the treatment of subjects with drug refractory recurrent symptomatic paroxysmal atrial fibrillation.

Arctic Front® Cardiac CryoAblation System, consisting of:

- Arctic Front® Cardiac CryoAblation Catheter in two balloon sizes
- Manual Retraction Kit
- The Freezor® *MAX* Cardiac CryoAblation Catheter in two curves Ref # 239F3 and 239F5
- Medtronic CryoCath CryoConsole

Medtronic may incorporate additional Medtronic CryoCath CryoConsoles, updated Freezor MAX and Arctic Front® Cardiac CryoAblation Catheters or updated CryoConsole software into this post-approval study as they receive appropriate license or regulatory approval and are released commercially by Medtronic, provided they do not affect the scientific soundness of the study.

4 METHODOLOGY

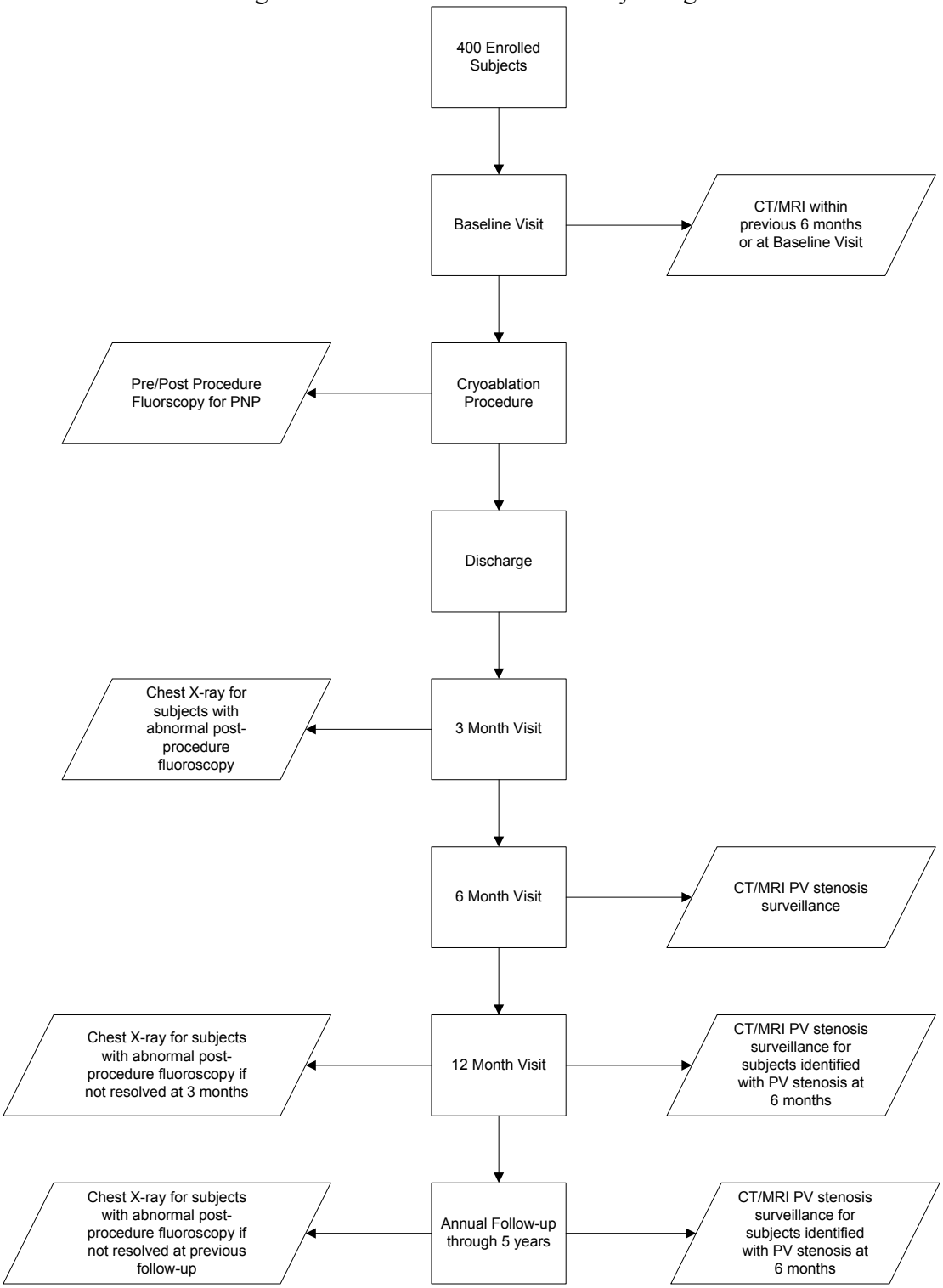
4.1 Study Design

The PAS is a prospective multi-center, non-randomized, single arm, controlled, unblinded clinical study designed to provide long-term safety and effectiveness of the Arctic Front® Cardiac CryoAblation System.

Safety and effectiveness will be evaluated against pre-specified performance criteria as determined by the sponsor and FDA. The criteria set in this study have been previously used to demonstrate safety and effectiveness in cryoablation and radio-frequency ablation for the treatment of paroxysmal atrial fibrillation.

The analyses of the primary effectiveness objective will take place once all the subjects with a study cryoablation procedure attempt have reached 36 months of follow-up post-cryoablation procedure. The analysis of the primary safety objective will take place once all the subjects with a study cryoablation procedure attempt have reached 12 months of follow-up post-cryoablation procedure. The analyses for the secondary objectives will take place once all subjects with a study cryoablation attempt have reached 60 months of follow-up post-cryoablation procedure. The overall study design is summarized in Figure 1.

Figure 1: STOP AF PAS Overall Study Design



4.2 Primary Effectiveness Objective

Demonstrate effectiveness (through 36 months) of the Arctic Front® Cardiac CryoAblation Catheter System, including the Freezor® MAX Cardiac Cryoablation Catheter by assessing the rate of subjects free of chronic treatment failure with paroxysmal atrial fibrillation who have failed one or more Atrial Fibrillation Drugs (AFDs).

Chronic treatment failure is defined as:

- Documented atrial fibrillation lasting longer than 30 seconds OR
- Intervention for atrial fibrillation (except for repeat cryoablation during the 90 day blanking period)

Intervention for atrial fibrillation is defined as: An invasive procedure intended for the definitive treatment of AF, including any ablation of the PVs or atrial triggers (other than protocol-specified ablation), interruption of AV nodal function, procedures to alter left atrial conduction or function such as the Maze procedure, or the implantation of an atrial pacemaker or atrial defibrillator; whether approved by relevant regulatory authorities or not for such indications; excluding electrical or pharmacologic cardioversion of arrhythmias and excluding procedures solely directed at the treatment of atrial flutter or atrial tachycardias. A reablation permitted under Section 5.12 of this protocol is not an AF intervention.

4.3 Primary Safety Objective

Demonstrate safety (through 12 months) of Arctic Front® Cardiac CryoAblation Catheter System, including the Freezor® MAX Cardiac Cryoablation Catheter by assessing the rate of subjects experiencing a Cryoablation Procedure Events (CPEs) with paroxysmal atrial fibrillation who have failed one or more Atrial Fibrillation Drugs (AFDs).

Cryoablation procedure event is defined in Table 2 below.

Table 2: Cryoablation Procedure Event

Cryoablation Procedure Events (CPE)	With onset between Day 0 and:
Access site complications requiring: Transfusion of 3 or more units or Surgical intervention or Permanent loss or functional impairment	Day 7
Cardiac damage (including MI)	Day 7
Pulmonary vein stenosis*	Through 12-months
Atrio-esophogeal fistula	Through 12-months
Embolic complications (including stroke)	Day 7
Arrhythmias	Day 7
Persistent phrenic nerve palsy**	Through 12-months
Death	Day 7

* CPE will be assessed at the completion of the follow-up visit, as determined by CT/MRI Core Lab.
** CPE will be assessed at the completion of the follow-up as determined by chest X-ray (insp/exp)

4.4 Secondary Objectives

The following are a list of secondary objectives, which are intended to provide additional information on the performance of the Arctic Front® Cardiac CryoAblation Catheter System. There will be no established performance requirements related to these secondary objectives required. The secondary objectives are as follows:

Safety Objective:

- Evaluate the proportion of subjects free from MAFE events at 1, 2, 3, 4 and 5 years

Major Atrial Fibrillation Event (MAFE): A MAFE is a serious adverse event (SAE) — which has not been categorized as a CPE—as set out in the following Table:

Table 3: Major Atrial Fibrillation Events

Major Atrial Fibrillation Events (MAFEs):
Cardiovascular deaths
Hospitalizations for (primary reason): AF recurrence or ablation Atrial flutter ablation (excluding Type I) Systemic embolization (not stroke) Congestive heart failure Hemorrhagic event (not stroke) Antiarrhythmic drug: initiation, adjustment or complication
Myocardial infarction (MI)
Stroke

Effectiveness Objective:

- Evaluate the proportion of subjects free of chronic treatment failure at 1, 2, 4 and 5 years

Cryoablation Objectives:

- Procedure parameters

4.5 Site Selection

Investigational sites that participated in the Continued Access Protocol for the Evaluation of Catheter Cryoablation in the Treatment of Paroxysmal Atrial Fibrillation (CAP-AF) will be invited to participate in the PAS. In addition, investigational sites that followed subjects with pulmonary vein (PV) stenosis or unresolved phrenic nerve injury (PNI) in STOP AF will be invited to participate.

The sponsor will also invite at least 30 investigational sites that are new users (non-STOP AF/CAP AF sites) of the Arctic Front® Cardiac CryoAblation Catheter System. The new user investigational sites will be selected from the pool of United States sites that have the following:

- Medtronic CryoCath CryoConsole that is compatible with the Arctic Front® Cardiac CryoAblation Catheter System and have completed the required product training
- Willingness to participate in protocol and precedural training, as requested,
- Sufficient staff (at least one primary investigator, one radiologist and study coordinator) and Medtronic support to execute and maintain

compliance to the protocol, including data collection and record retention requirements
- Acknowledgement of, and agreement to, comply with applicable regulatory and local requirements governing clinical study conduct
- Site has the ability to submit data via Oracle Clinical database

Additionally, Investigational sites must have the qualified personnel and equipment to perform the protocol specified surveillance for recurrent atrial fibrillation, pulmonary vein stenosis and phrenic nerve injury as described in Section 5.10 of this protocol as well as all other study related duties. All investigational sites will complete the required protocol training prior to enrolling subjects in the study.

All applicable physicians will be asked to participate in the study.

4.6 Subject Selection

Subjects who have a diagnosis of paroxysmal atrial fibrillation will be considered for the study based on the inclusion and exclusion criteria. Subjects are considered enrolled upon signing the Informed Consent Form and must be consented prior to any study driven testing. The date the subject signed the consent form and privacy authorization (if required) must be recorded.

Subjects that were enrolled and treated in CAP-AF will be asked to participate in the follow-up phase of this PAS and are exempt from the inclusion and exclusion criteria for this study.

FDA requested the sponsor attempt to enroll STOP AF subjects into the STOP AF PAS that demonstrated PV stenosis or unresolved PNI at the conclusion of the STOP AF pivotal as defined in the STOP AF protocol. These subjects are exempt from the inclusion and exclusion criteria for this study.

Sites will be required to document effort to enroll CAP AF and STOP AF subjects into the STOP AF PAS.

Enrolled subjects may participate in other clinical trials that are not likely to impact the scientific soundness of this PAS. Sites are required to obtain written approval from Medtronic prior to enrolling subjects already participating in an ongoing clinical trial or enrolling an existing PAS subject in another clinical trial.

4.6.1 Inclusion Criteria:

For inclusion in the study, subjects must fulfill **ALL** of the following criteria:

- Documented PAF:
  - Diagnosis of paroxysmal atrial fibrillation (PAF), AND

  - 2 or more episodes of AF during the 3 months preceding the Consent Date, at least 1 of which must be documented with a tracing
- Age 18 years or older
- Failure for the treatment of AF (effectiveness or intolerance) of one or more of the following drugs indicated in the treatment of PAF: flecainide, propafenone, sotalol or dofetilide.

4.6.2 Exclusion Criteria:

ANY of the following is regarded as a criterion for excluding a subject from the study:

- Any previous left atrial (LA) ablation (except permissible retreatment subjects)
- Any previous LA surgery
- Current intracardiac thrombus (can be treated after thrombus is resolved)
- Presence of any pulmonary vein stents
- Presence of any pre-existing pulmonary vein stenosis
- Pre-existing hemidiaphragmatic paralysis
- Anteroposterior LA diameter > 5.5 cm by TTE
- Presence of any cardiac valve prosthesis
- Clinically significant mitral valve regurgitation or stenosis
- Myocardial infarction, PCI / PTCA or coronary artery stenting which occurred during the 3 month interval preceding the Consent Date
- Unstable angina
- Any cardiac surgery which occurred during the 3 month interval preceding the Consent Date
- Any significant congenital heart defect corrected or not (including atrial septal defects or pulmonary vein abnormalities but not including minor PFO)
- NYHA class III or IV congestive heart failure
- Left ventricular ejection fraction (LVEF) < 40%
- 2º (Type II) or 3º atrioventricular block
- Presence of a permanent pacemaker, biventricular pacemaker, atrial defibrillator or any type of implantable cardiac defibrillator (with or without biventricular pacing function)
- Brugada syndrome
- Long QT syndrome

- Arrhythmogenic right ventricular dysplasia
- Sarcoidosis
- Hypertrophic cardiomyopathy
- Known cryoglobulinemia
- Uncontrolled hyperthyroidism
- Any cerebral ischemic event (strokes or TIAs) which occurred during the 6 month interval preceding the Consent Date.
- Any woman known to be pregnant
- Life expectancy less than one (1) year
- Current or anticipated participation in any other clinical trial of a drug, device or biologic during the duration of this study
- Unwilling or unable to comply fully with study procedures and follow-up

4.7 Minimization of Bias

Potential sources of bias in this study may result from selection of subjects, treatment of subjects, and evaluation of study data. The following methods have been incorporated into the study to minimize potential bias include (not limited to these):

- Subjects will undergo a rigorous screening to confirm eligibility for enrollment with defined inclusion/exclusion criteria prior to enrollment
- All centers and geographies will use the same version of the Clinical Investigational Plan and CRFs
- Data collection requirements and study procedures will be standardized across all geographies
- All investigational site personnel and Medtronic personnel will be trained on their respective aspects of the study using standardized training materials
- All investigational site personnel will be trained on and required to follow the Clinical Investigational Plan
- An independent adjudication committee will be utilized to regularly review and adjudicate reported adverse events and endpoints
- All study investigators will be required to meet 21 CFR Part 54, Financial Disclosure by Clinical Investigators, to identify potential bias due to financial interest in the outcome of the study

5 STUDY PROCEDURES

All clinical investigators performing a cryoablation procedure must be trained in the handling of Arctic Front® Cardiac CryoAblation Catheter and must receive protocol training prior to any study procedures.

Center personnel who consent patients and/or participate in the follow-up visits must be trained by Medtronic.

5.1 Equipment requirements

The following equipment must be available at each center to support study activities:

- Medtronic CryoCath CryoConsole
- Arctic Front® Cardiac CryoAblation Catheter in two balloon sizes
- Manual Retraction Kit
- Freezor® MAX Cardiac CryoAblation Catheter in two curves

The maintenance and calibration of the equipment as listed above will be assessed by the participating center following their normal processes. Clinical monitors will not monitor maintenance or calibration schedules.

5.2 Informed Consent Process

Patient informed consent is defined as legally effective, documented confirmation of a subject's (or their legally authorized representative or guardian) voluntary agreement to participate in a particular clinical investigation after information has been given to the subject on all aspects of the clinical investigation that are relevant to the subject's decision to participate.

When the patient has consented to participate in the trial, they are considered to be an enrolled subject.

Each investigational center's Ethics Board will be required to approve the Clinical Investigation Plan (CIP), Informed Consent (IC) and any subject recruitment materials. Refer to for the sample patient informed consent form(s). Any changes to the patient informed consent must be approved by Medtronic and the Ethics Board reviewing the application before being used to consent a prospective study subject. The document(s) should be controlled (i.e. versioned and/or dated) to ensure it is clear which version(s) were approved by the Ethics Board.

Prior to initiation of any study-specific procedures, subjects (or their legally authorized representative or guardian) must sign and date the HIPAA/data protection authorization/or other privacy language where required by law and the Ethics Board and Medtronic approved Informed Consent. The Informed Consent form and HIPAA/data protection authorization/or other privacy language where

required by law, must be given to the subject (or their legally authorized representative or guardian) in a language he/she is able to read and understand.

The process of obtaining patient informed consent shall:

- Avoid coercion and undue influence of subjects to participate
- Not waive or appear to waive subject's legal rights
- Use language that is non-technical and understandable to the subject
- Provide ample time for the subject to consider participation
- Include a dated signature of the subject acknowledging that their participation in the study is voluntary

If the patient informed consent is obtained the same day the subject begins participating in study-related procedures, it should be documented in the subject's case history that consent was obtained prior to participation in any study-related procedures.

In the event the subject cannot read and/or write, witnessed (impartial third party) informed consent will be allowed, provided detailed documentation of the process is recorded in the subject's case history and the witness signs and dates the patient informed consent.

The original or a copy of the signed patient informed consent must be filed in the hospital/clinical chart or with the subject's study documents. A copy of the signed patient informed consent and authorization/or other privacy language where required by law must be provided to the subject. When a patient signs and dates the STOP AF PAS informed consent, he/she is considered a subject enrolled in the study.

The patient informed consent form and the signed patient informed consent and authorization/or other privacy language (where required by law) must be available for monitoring and auditing.

5.3 Data Collection Overview

Clinical data will be collected at the time points detailed in Table 4.

Table 4: Data Collection/Study Procedure Requirements at Subject Visits

		Cryoablation Procedure			Repeat Cryoablation Procedure (0-90 days)							
	Baseline	Procedure	Post-procedure	Discharge	Baseline	Procedure	Post-procedure	Discharge	3 month	6 and 12 month	2, 3, 4 and 5 year	Termination
Consent	X				X							
Incl/Excl Criteria	X				X							
History	X											
Physical exam	X			X	X			X	X	X	X	X
Anticoagulation Use	X			X	X			X	X	X	X	X
Arrhythmic Sx review	X				X				X	X	X	X
Use of AFDs	X				X				X	X	X	X
12 lead ECG	X			X	X			X	X	X	X	X
TTE	X(1)			X	X(1)			X				
MRI or CT	X(1)									X(3,4)	X(3,4)	X(3,4)
24 hour Holter monitoring										X		
48 hour Holter monitoring										X(6)	X	X
SF-12 Health Survey	X(7)									X	X	X
TEE		X(2)		X		X(2)		X				
Chest X-ray (insp/exp)									X(5)	X(5)	X(5)	X(5)
Fluoroscopy		X	X			X	X					
AE review		X	X	X	X	X	X	X	X	X	X	X

1. Performed during the 6 month interval preceding the Consent Date, or between the Consent Date and Procedure Date
2. Performed within 7 days prior to the Procedure
3. Follow-up PV imaging technology (CT or MRI) performed at follow-up visits must be the same type as used for baseline
4. Only if CT/MRI at 6 month follow-up demonstrated PV stenosis in one or more pulmonary veins
5. Performed at the 3 month follow-up for subjects whose post-procedural fluoroscopy demonstrated study-related phrenic nerve palsy. If phrenic nerve palsy is present at

the 3 month visit, a chest X-ray (inspiration/expiration) is required at 12 month follow-up visit. If phrenic nerve palsy persists at the 12 month visit, a chest x-ray is required at the each annual (24-60 months) follow-up until resolved.

6. Performed at the 12 month follow-up visit.
7. Only subjects that will be receiving their initial ablation procedure in the STOP AF PAS.

5.4 Subject Follow-Up Schedule

Regular follow-ups are necessary to monitor the condition of subjects. Subjects with a study procedure attempt will be followed through 60 months post study cryoablation procedure attempt.

If a follow-up visit falls outside the prescribed window, a study deviation must be reported and the original follow-up window must be maintained for subsequent visits. Follow-up visits outside the window will be used in the final analysis.

Follow-up visit windows are listed in Table 5. All windows are based on days post - study cryoablation procedure attempt.

Table 5: Subject Follow-up Windows

Visit	**Window** ***(Days post study cryoablation procedure attempt)***		
	Window Start (# of days)	Target (# of days)	Window End (# of days)
Month 3	76	90	104
Month 6	166	180	194
Month 12	365	365	395
Month 24	700	730	760
Month 36	1,095	1,095	1,125
Month 48	1,430	1,460	1,490
Month 60	1,795	1,825	1,855

5.5 Baseline

The following baseline evaluations will be performed after consent, unless previously performed as part of routine clinical evaluations within the specified windows:

Within 6 months prior to the Consent Date:

1. Documented Trans-thoracic Echocardiogram (TTE) performed during the 6 month interval preceding the Consent Date, or between Consent and Start Dates
2. An MRI or CT scan of the four PVs or their anomalous equivalent performed during the 6 month interval preceding the Consent Date, or between Consent and Start Dates

Performed within 1 month prior to the Consent Date:

1. Medical history, including
    a. assessment of risk factors, NYHA cardiac function class, systemic history and cardiovascular medical history
    b. assessment of atrial fibrillation symptoms and other arrhythmic episodes that have occurred in the 3 month interval preceding the Consent Date
    c. history of AF with documentation, including date of onset
    d. number of cardioversions and AF-related hospitalizations that have occurred in the 12 months preceding the Consent Date.
    e. medication history regarding prior and current use of AFDs, including any of the following AFDs: flecainide, propafenone, sotalol, dofetilide, amiodarone.
    f. assessment of all factors specified for evaluation under Inclusion Criteria and Exclusion Criteria
2. Physical examination and vital signs
3. 12 lead ECG

Performed after Consent Date

1. SF-12 Health Survey

Performed within 7 days prior to the Start Date (procedure date):

1. A transesophageal echocardiogram (TEE) assessing potential thrombus in the heart within 7 days prior to the Start Date

5.6 Cryoablation Procedure

Prior to the cryoablation procedure, the Investigator will review the procedural steps in this protocol and the relevant documentation for the Arctic Front® Cardiac CryoAblation Catheter, the Freezor® MAX Cardiac Cryoablation Catheter and the Cryoablation console. In addition, the Investigator will:

1. Prior to the first cryoablation application, the Investigator will make a fluoroscopic recording of inspiratory and expiratory movement of the diaphragm.
2. During the procedure the investigator will document the following:
    a. Catheter used for each cryoapplication (i.e. Arctic Front, Freezor Max or RF)
    b. Temperature for each cryoapplication
    c. Duration of each cryoapplication
    d. Vein location for each cryoapplication (e.g. Right superior pulmonary vein)
    e. Use of phrenic nerve pacing for each cryoapplication
3. After the last cryoablation application, the investigator will make a fluoroscopic recording of the inspiratory and expiratory movement of the diaphragm.

5.6.1 Other Ablations

1. Occasional subjects will have cardiac rhythm abnormalities requiring treatment detected during the cryoablation procedure. Whenever possible, the experimental cryoablation devices will be used, however when necessary for subject welfare, other commercially available devices may be utilized at the Investigator's discretion. This may include right / left atrial flutter or atrial fibrillation triggers.
2. Such ablations will be fully documented in the relevant CRF. Post Procedure Evaluations
3. Before leaving the EP Lab:
   a. total procedure duration, total elapsed fluoroscopy duration and first cryocatheter insertion / last cryocatheter removal times (total cryocatheter insertion time) will be recorded.
   b. procedure duration and elapsed fluoroscopy duration during non-cryo applications will be recorded (if any).
   c. the use of any adjunctive mapping or visualization devices will be recorded on the relevant CRF.

5.6.2 Discharge Procedures

At or shortly before discharge:

1. Assessments: All subjects will have the following assessments prior to discharge:
   a. physical examination and vital signs
   b. 12 lead ECG
   c. Transthoracic echocardiogram within 72 hours post-procedure
   d. screening for adverse events
2. Anticoagulation: Subjects will have anticoagulation treatment determined by the Investigator according to established guidelines.
3. Instructions: The subject will be given written instructions on the handling and reporting of any symptomatic events throughout the follow-up period.
4. Post ablation AF drug regimens: the use of AF drugs during this investigation is determined by the clinical judgment of the Investigator. Any use of membrane-active AFDs (Class Ia, Ic, III) will be documented in the CRF. These drugs include quinidine, procainamide, disopyramide, flecainide, propafenone, moricizine, amiodarone, dofetilide, ibutilide and sotalol.

5.7 Scheduled Follow-up Visits

5.7.1 Three, Six and Twelve Month Follow-up Visits

Subjects must be seen in person. The following data/procedures will be completed at each follow-up visit.

- Physical exam

- 12 lead ECG
- Medications
- Adverse event collection
- 24 hour Holter monitoring (6 month)
- 48 hour Holter monitoring (12 month)
- SF-12 Health Survey (6 and 12 month)
- Signs/symptoms review for arrhythmias
- Intercurrent episodes of medical care suggestive of arrhythmia including hospitalizations, office or ER visits, or any AF-related procedures such as cardioversion or additional ablation
- Treatment with AFD
- Anticoagulation use
- For any subject whose post-procedural fluoroscopy demonstrated study-related phrenic nerve palsy, a follow up chest X-ray including inspiration / expiration films will be performed at the 3 month follow-up visit
- 12 month follow-up visit chest X-ray (inspiration / expiration) required if phrenic nerve palsy was unresolved at 3 month follow-up visit
- For any subject whose 6 month CT/MRI demonstrated PV stenosis, a CT/MRI scan will be performed at the 12 month follow-up.

5.7.2 Two through Five Year Follow-up Visits

Subjects must be seen in person. The following data/procedures will be completed at each follow-up visit. Subjects are exited from the study at the 60 month visit.

- Physical exam
- 12 lead ECG
- Medications
- Adverse event collection
- 48 hour Holter monitoring
- SF-12 Health Survey
- Signs/symptoms review for arrhythmias
- Intercurrent episodes of medical care suggestive of arrhythmia including hospitalizations, office or ER visits, or any AF-related procedures such as cardioversion or additional ablation
- Treatment with AFD
- Anticoagulation use

- Chest X-ray (inspiration / expiration) required if phrenic nerve palsy unresolved at previous follow-up visit
- For any subject whose 6 month CT/MRI demonstrated PV stenosis, a CT/MRI scan will be performed.

5.8 Unscheduled Follow-up Visits

For any subject performing an unplanned office visit, assessments will be performed as follows:

- Physical exam
- 12 lead ECG
- Medications
- Adverse event collection
- Signs/symptoms review for arrhythmias
- Intercurrent episodes of medical care suggestive of arrhythmia including hospitalizations, office or ER visits, or any AF-related procedures such as cardioversion or additional ablation
- Health care utilization
- Treatment with AFD
- Anticoagulation use

5.9 Termination Follow-up Visits

For any subject not completing 36 months of clinic follow-up (e.g., due to withdrawal) termination assessments will be performed as follows:

- Physical exam
- 12 lead ECG
- Medications
- Adverse event collection
- 48 hour Holter monitoring
- SF-12 Health Survey
- Signs/symptoms review for arrhythmias
- Intercurrent episodes of medical care suggestive of arrhythmia including hospitalizations, office or ER visits, or any AF-related procedures such as cardioversion or additional ablation
- Treatment with AFD
- Anticoagulation use
- For any subject whose post-procedural fluoroscopy demonstrated study-related phrenic nerve palsy, a follow up chest X-ray (inspiration / expiration films) will be performed at the Termination

follow-up visit if phrenic nerve palsy was unresolved at the 3 month or previous follow-up visit.

-
- For any subject whose 6 month CT/MRI demonstrated PV stenosis, a CT/MRI scan will be performed at the Termination follow-up visit.

5.10 Visit Procedure Details

5.10.1 Physical exam

The physical exam will include the following:

- Vital signs (blood pressure/heart rate)
- Check of body systems
  - Neck – JV pressure
  - Lungs – auscultation
  - Cardiovascular
  - Abdomen

5.10.2 12 lead ECG

A 12 lead ECG must be completed and analyzed by the investigator.

5.10.3 Medications

Information regarding medications will be collected including the purpose for their use and, start and stop dates and dosage.

5.10.4 Adverse event collection

If a subject presents with symptoms at or outside of their scheduled follow-up the center is required to report any unreported adverse events. In addition, any changes (e.g. actions taken, change in outcomes) to previously reported unresolved adverse events must be reported.

5.10.5 Signs/symptoms review for arrhythmias

Assess for signs/symptoms of arrhythmias since last visit. Subjects that present with symptoms believed to be due to atrial fibrillation, but was not captured on ECG, will be provided with an event recorder for 30 days to capture symptomatic atrial fibrillation

5.10.6 24 Hour Holter monitoring

At the 6 month (window ± 2 weeks) a 24 hour Holter monitor will be obtained.

5.10.7 48 Hour Holter Monitoring

The annual follow-ups at months 12, 24, 36, 48 and 60, a 48 hour Holter monitor will be required.

5.10.8 SF-12 Health Survey

At baseline, 6 month, 12 month and annual visits through 60 months, subjects will be asked to complete the SF-12 Health Survey.

5.10.9 Health Care Utilization

During the course of the study, Medtronic will ask investigational sites to provide certain elements from the UBO4 and 1500 forms for health care utilization analyses. The frequency of this data collection will be determined by the changes in subject health status that requires use of the health care system.

5.10.10 CT/MRI Imaging for Pulmonary Vein Stenosis

At the 6 month follow-up visit, subjects will undergo an MRI or CT scan (same technology as the baseline assessment) of all PVs or their anomalous equivalents. For any subject that has > 50% reduction in baseline PV area, as determined by a site radiologist, an additional review will be performed by an independent Core Lab to confirm protocol defined PV stenosis of > 75% reduction in baseline PV area. For those subjects with core lab confirmed PV stenosis an additional MRI or CT scan will be repeated at 12 months and annually through 60 months.

5.10.11 Chest X-ray for Phrenic Nerve Palsy

For any subject whose post-procedural fluoroscopy demonstrated study-related phrenic nerve palsy, a follow up chest X-ray including inspiration / expiration films will be performed at the 3 month follow-up and annually until resolved or subject has completed the 60 month follow-up. All chest X-rays for study related phrenic nerve palsy will be analyzed by a site radiologist.

5.11 Recurrence of Atrial Fibrillation

If a subject presents with symptoms at or outside of the scheduled follow-up visits, the center is required to report any documented recurrence of AF. This documentation must be provided to the sponsor and additional source documents may be requested.

Documentation of AF must include at least one of the following per standard center procedures:

- ECG
- TTM
- Holter
- Rhythm strip

5.12 Permissible Retreatment of Study Subjects

All Study Subjects may have one repeat cryoablation procedure within Days 0 – 90 under this protocol if all the following criteria are met:

1. Informed Consent: If the original Informed Consent does not cover this repeat cryoablation procedure, then Informed Consent will be obtained for this procedure.
2. Inclusion / Exclusion criteria for repeat cryoablation procedure:
   a. The subject has either of the following:
      i. Failure to isolate one or more PVs during the initial cryoablation procedure or
      ii. Recurrent AF
   b. The subject has not had any other ablation procedure in the LA between the first cryoablation and the proposed repeat cryoablation.
   c. The subject continues to meet Study Exclusion Criteria, where the reablation procedure date is substituted for "Start Date" and "Consent Date".
3. Baseline reablation assessments are performed as follows:
   a. Baseline Evaluations.
   b. Assessment of NYHA cardiac function class
   c. If the TTE performed for the first cryoablation procedure was obtained more than 6 months prior to the proposed date for the second procedure, then another TTE
   d. Another TEE within 7 days prior to the reablation date
4. Study Status post Reablation: Reablated Subject's Start Date and study-specified intervals, procedures and assessments remain the same. A reablation of a study subject under this Section is not an AF Intervention.

5.13 Study Exit

Prior to an early exit of a subject from the study, all efforts should be made to continue following the subject until all unresolved serious, device and procedure

related adverse events are resolved or they are considered to be unresolved, no further actions planned. Prior to exit every attempt should be made to determine and report the status of any unresolved adverse events. Prior to exit every attempt should be made to determine and report the status of the any recurrent atrial fibrillation.

Once a subject has been exited from the study, there will be no further follow-up or attempts to collect data on the subject. All data available through the time of the subject's exit will be used for analysis.

Subjects are urged to remain in the study as long as possible, but may be exited from the trial for any of the following situations:

- Subject has completed follow-up
- Subject lost to follow-up
- Subject death
- Subject did not meet inclusion/exclusion criteria after consent
- Subject chooses to withdraw (e.g., consent withdrawal, relocation to another geographic location)
- Investigator deems withdrawal necessary (e.g., medically justified, inclusion/exclusion criteria not met, failure of subject to maintain adequate study compliance)
- The sponsor decides the study will be closed or a particular center will be closed

5.14 Lost to Follow-Up

In the case that the subject is determined to be lost to follow-up, the following contact attempts should be made; one phone message to subject, one phone message to subject through a contact person and one letter. Regulations set forth by the governing IRB/MEC must be followed.

5.15 Subject Follow-up after Withdrawal

Investigational sites will notify the sponsor of a subject's intention to withdraw from the study. The subject's atrial fibrillation status will be collected prior to the subject exiting the study. If a subject is withdrawn from the study prior to their 60 month visit, no further study visits will occur for the subject and no further study data will be collected after the date of withdrawing from the study.

5.16 Medication Restrictions

All medications are permitted in this study with following exceptions:

- Investigational drugs that may confound the study results

6 STUDY DEVIATIONS

A study deviation is defined as an event within a study that did not occur according to the Clinical Investigation Plan or the Clinical Trial Agreement.

Prior approval by the Medtronic Clinical Study Manager or designee is expected in situations where the investigator anticipates, contemplates, or makes a conscious decision to deviate. Prior approval is not required when a deviation is necessary to protect the life or physical well being of a subject in an emergency or in unforeseen situations beyond the investigator's control (*e.g.* subject failure to attend scheduled follow-up visits, inadvertent loss of data due to computer malfunction, inability to perform required procedures due to subject illness, etc.).

For medically justifiable conditions which preempt a subject's ability to complete a study-required procedure, it may be permitted to complete only one deviation CRF which will apply to all visits going forward. This may also apply for other unforeseen situations (e.g. the subject permanently refuses to complete a study required procedure, and the data will not contribute to the primary end point analysis, etc.). However, prior approval from Medtronic is required for such situations.

All study deviations must be reported to Medtronic regardless of whether medically justifiable, pre-approved by Medtronic, an inadvertent occurrence, or taken to protect the subject in an emergency. The deviation must be recorded with an explanation for the deviation and corrective/ preventative action(s).

In the event the deviation involves a failure to obtain a subject's consent, or is made to protect the life or physical well being of a subject in an emergency, the deviation must be reported to the Institutional Review Board (IRB) as well as Medtronic within five (5) working days. Reporting of all other study deviations should comply with IRB policies and/or local laws and must be reported to Medtronic as soon as possible upon the center becoming aware of the deviation. Reporting of deviations must comply with IRB/ MEC policies, local laws, and or regulatory agency requirements. Refer to Investigator Reports, Table 13 for geography-specific deviation reporting requirements and timeframes for reporting to Medtronic and/or regulatory bodies.

Medtronic is responsible for analyzing deviations, assessing their significance, and identifying any additional corrective and/or preventive actions (e.g. amend the Clinical Investigation Plan, conduct additional training, terminate the investigation, etc.). Repetitive or serious investigator compliance issues may represent a need to initiate a corrective action plan with the investigator and site, and in some cases, necessitate suspension of enrollment until compliance is obtained or ultimately terminating the investigator's participation in the study. Medtronic will provide center-specific reports to investigators summarizing information on deviations that occurred at the investigational site on a periodic basis.

7 ADVERSE EVENTS

Timely, accurate, and complete reporting and analysis of safety information for clinical studies are crucial for the protection of subjects, investigators, and the sponsor. Reporting and analysis of safety data are mandated by regulatory authorities worldwide. Medtronic has established procedures in conformity with worldwide regulatory requirements to ensure appropriate reporting of safety information. This study is conducted in accordance with these procedures and regulations.

7.1 Adverse Event Assessment

All adverse events (AEs) and adverse device effects (ADE's) will be reported in all geographies (i.e. US and Canada) throughout the study duration. Exceptions include:

- Documented pre-existing conditions unless the nature or severity of the condition has worsened.
- Recurrence of AF event unless an action is taken.
- Unavoidable AEs unless the AE worsens or is present outside the stated timeframe listed in Table 6

Information reported about an AE will include date of onset, a description of the event, diagnosis, relationship of the event to a procedure, relationship of the event to each device, actions taken as a result of the event, and the outcome of the event. Each diagnosis must be reported as a separate event.

Subject deaths are also required to be reported. Refer to Section 7.4 for study requirements related to subject death.

Managing AE updates and resolving AEs

For any changes in status of a previously reported adverse event (i.e. change inactions taken, change in outcome, change in relatedness), an adverse event update must be completed. All AEs must be followed until the AE has been resolved, is unresolved with no further actions planned, the subject exits the study or until study closure, whichever occurs first.

In the event that a subject is exited from the study prior to study closure, all efforts should be made to continue following the subject until all unresolved AEs are resolved or are considered unresolved with no further actions planned.

At the time of study closure, all AEs with an outcome of "unresolved, further actions or treatment planned" must be reviewed and an AE update must be provided. At a minimum, if there are no changes to the description, relatedness,

or actions taken, the outcome must be updated to reflect that it is unresolved at time of study exit/death/study closure.

7.2 Adverse Event Definitions, Classification and Reporting

7.2.1 Adverse Event Definitions

Definitions provided in Table 6 will be used throughout this study for the purpose of collecting, classifying and reporting adverse events:

Table 6: Adverse Event Definitions

General	
Adverse Event (AE)	Any untoward medical occurrence in a subject NOTE: This definition does not imply that there is a relationship between the Adverse Event and the device under investigation.
Hospitalization	A hospital admission lasting more than 24 hours or which includes an overnight admission.
Seriousness	
Serious Adverse Event (SAE)	An Adverse Event that a) led to a death, or b) led to a serious deterioration in the health of the subject that • Resulted in a life-threatening illness or injury, or • Resulted in permanent impairment of a body structure or a body function, or • Required in-patient hospitalization >48 hours or prolongation of existing hospitalization, or • Resulted in medical or surgical intervention to prevent, permanent impairment to body structure or a body function, or c) led to fetal distress, fetal death or a congenital abnormality or birth defect

Complication	An adverse event that results death, involves any termination of significant device function, or requires an invasive intervention • **Noninvasive**: Noninvasive, when applied to a diagnostic device or procedure, means one that does not by design or intention: (1) Penetrate or pierce the skin or mucous membranes of the body, the ocular cavity, or the urethra, or (2) enter the ear beyond the external auditory canal, the nose beyond the nares, the mouth beyond the pharynx, the anal canal beyond the rectum, or vagina beyond the cervical os. For purposes of this part, blood sampling that involves simple venipuncture is considered noninvasive, and the use of surplus samples of body fluids or tissues that are left over from samples taken for non-investigational purposes is also considered noninvasive. (21 CFR 812.3(k))
Observation	Any adverse event that is not a complication.
Relatedness	
Cryoablation Procedure related	An Adverse Event that occurs due to any procedure related to the study cryoablation procedure.
Procedure related	An Adverse Event that occurs due to any other procedure related to the study (i.e. EP study).
Device related	**Arctic Front® Cardiac CryoAblation Catheter System catheter related:** An adverse event that results from the presence or performance (intended or otherwise) of the Arctic Front® Cardiac CryoAblation Catheter System **Other related:** An adverse event that results from the presence or performance (intended or otherwise) of any other device / tool used
Timing	
Ablation Procedure AE	An adverse event that occurs during the ablation procedure, after introduction of the study catheter into the vasculature and prior to completion of skin closure.
Post-ablation Procedure AE	An adverse event that occurs after the completion of skin closure for the ablation procedure.
Unavoidable AE	An adverse event inherent to a surgical procedure that is expected to occur in all subjects for a projected duration according to the investigator's opinion, including, but not limited to the list provided below. Unavoidable AEs are not reportable AEs. Onset of any of these events occurring after the specified timeframes and/or events lasting longer than the

specified timeframe if onset is at the time of the surgery should be reported as adverse events under the above definitions.

Unavoidable AEs	
Event Description	**Time (Hours) from the Surgical Procedure**
Anesthesia related nausea/vomiting	24
Low-grade fever (<100°F or < 37.8°C)	48
Incisional pain	72
Mild to moderate bruising / ecchymosis	168
Sleep problems (insomnia)	72
Back pain related to lying on the table	72
Shoulder pain/discomfort/stiffness related to shoulder immobilization during procedure	72

7.3 Adverse Event Classification and Reporting

AEs will be classified according to the definitions provided. In order to meet the requirements of the regulatory agencies, each event will be classified by the investigator according to standard regulatory definitions.

Upon receipt of adverse events at Medtronic, a Medtronic representative will review the adverse event for completeness and accuracy and when necessary will request clarification and/or additional information from the Investigator. Medtronic will utilize MedDRA, the Medical Dictionary for Regulatory Activities, to assign a MedDRA term for each adverse event based on the information provided by the investigator.

Regulatory reporting of AEs will be completed according to local regulatory requirements. Refer to Table 9 and Table 10 for a list of required investigator and Medtronic reporting requirements and timeframes. It is the responsibility of the Investigator to abide by the AE reporting requirements stipulated by the IRB or MEC.

A listing (Foreseeable Adverse Event List (FAL)) of adverse events associated with the use of market-approved cryoablation systems or cryoablation procedure that have been observed in previous studies and may be experienced by subjects can be found in the product labeling. This list may help to assess if an AE is unexpected in nature.

Adverse Events and Deaths will be classified according to the standard definitions as outlined below:

Table 7: Adverse Event and Subject Death Classification Responsibilities

What is Classified	Who Classifies	Classification Parameters
Timing of the Event	Investigator	During study cryoablation procedure, Post study cryoablation procedure
Relatedness	Investigator	Arctic Front® Cardiac CryoAblation Catheter System, CryoConsole, study cryoablation procedure, other procedures
Severity	Investigator	SAE
	Sponsor	CPE, MAFE and Complication or Observation*
Diagnosis	Investigator	Based on presenting signs and symptoms and other supporting data
	Sponsor	MedDRA key term assigned based on the data provided by Investigator
Death Classification[1]	Investigator	Sudden Cardiac, Non-sudden Cardiac, Non-cardiac, Unknown
Event Adjudication[2]	Adverse Event Adjudication Committee (AEAC)	Adjudicates All of the Above

[1]Deaths will only be adjudicated to relatedness and death classification. All other adjudication information will be taken from the corresponding AE with an outcome of 'death'
[2]The AEAC may not adjudicate the following: timing of the event or MedDRA key term.
* Complication or Observation will apply to only system and procedure related adverse events

7.4 Subject Death

7.4.1 Data Collection

All subject deaths must be reported by the center to Medtronic as soon as possible after the center first learns of the death. The adverse event that lead to the death must be reported

A copy of the death certificate, if available and allowed by state/local law, should be sent to the in-house Medtronic clinical study team. When a death occurs in a hospital, a copy of the physician's dictated death summary report and all relevant hospital records should be sent to the in-house Medtronic clinical study team, if available. If an autopsy is conducted, the autopsy report should also be sent to the in-house Medtronic clinical study team. When the death occurs at a remote site, it is the investigative center's responsibility to attempt retrieval of information about the death. In summary, the following data will be collected:

- Date of death
- Detailed description of death
- Cause of death
- Relatedness to device
- Relatedness to procedures
- Death certificate (if available and allowed by state/local law)
- Death summary/hospital records (if available and allowed by state/local law)
- Autopsy report (if available and allowed by state/local law)

7.4.2 Classification and Reporting

Sufficient information will be required in order to properly classify the subject's death. The Investigator shall classify each subject death per the following definitions found in Table 8 Regulatory reporting of Subject Deaths will be completed according to local regulatory requirements. Refer to Table 9 and Table 10 for a list of required investigator and sponsor reporting requirements and timeframes.

Table 8: Subject Death Classification Definitions

Cardiac Death	A death directly related to the electrical or mechanical dysfunction of the heart.
Non-cardiac Death	A death not classified as a cardiac death.

Sudden Cardiac Death (SCD)	Natural death due to cardiac causes, heralded by abrupt loss of consciousness within one hour of the onset of acute symptoms; preexisting heart disease may have been known to be present, but the time and mode of death are unexpected. If time of onset cannot be determined, SCD will alternatively be defined as any unexpected cardiac death occurring out of the hospital or in the emergency room as dead on arrival.
Non-sudden Cardiac Death	All cardiac deaths that are not classified as sudden deaths, including all cardiac deaths of hospitalized subjects on inotropic support.
Unknown	Unknown death classification is intended for use only when there is insufficient or inadequate information to classify the death.

7.5 Adverse Event Adjudication Committee (AEAC) Review

At regular intervals, an independent Adverse Event Adjudication Committee (AEAC) will conduct a medical review of all adverse events and deaths for subjects participating in the study. This committee will also adjudicate events for endpoint considerations (CPE and MAFE).

The AEAC will consist of up to three non-Medtronic employed physicians, including an AEAC chairperson. At least three AEAC members must adjudicate, at a minimum, all deaths, serious AEs, device / procedure related AEs and events for endpoints. All other AEs must be adjudicated by at least one physician member of the AEAC.

Medtronic personnel may facilitate and participate in an AEAC meeting but will be non-voting members.

Medtronic will provide the AEAC with the Investigator's description and classification of each AE in addition to the MedDRA key term. The AEAC is responsible for reviewing the investigator's assessment and classification of each event, and adjudicating a final classification.

If the AEAC disagrees with the investigator's classification of the event, the rationale will be provided to the investigator. If the investigator agrees with the AEAC's adjudication, the case report form documenting the AE or AE update will be updated accordingly. If the investigator does not agree with the AEAC's adjudication, both determinations will be provided within the final report, however the AEAC's adjudication will be used for data analysis purposes

7.6 Medical Device Reporting Requirements for User Facilities

Per FDA regulations, Device User Facilities are required to report Medical Device Reports (MDR) on market approved products (21 CFR 803, subpart C)

A Device User Facility is defined as a hospital, an ambulatory surgical facility, a nursing home, an outpatient treatment facility, or an outpatient diagnostic facility which is not a physician's office.

7.7 Investigator Adverse Event Records and Reporting Requirements

Adverse Events will be recorded and reported according to local regulatory requirements. Refer to for investigator adverse event reporting requirements. It is the responsibility of the Investigator to abide by the adverse event reporting requirements stipulated by the centers' IRB/MEC.

Table 9: Investigator Adverse Event Reports

Report	Submit To	Description
Serious Adverse Event	Sponsor	Immediately after the Investigator first learns of event
	MEC/IRB	Reporting time frame as per local requirement
Adverse Device Effect (ADE) Other Adverse Device Effect	Sponsor	Immediately after the Investigator first learns of event
	MEC/IRB	Reporting time frame as per local requirement
All Other Adverse Events	Sponsor	Submit in a timely manner after the investigator first learns of the event
	MEC/IRB	Submit to MEC/IRB per local reporting requirement
Medical Device Reporting (Marketed Product)	FDA (US)	A report must be submitted to the sponsor as soon as practicable but no more than 10 work days after the day that the investigator become aware of information, from any source, that reasonable suggests that a device has or may have caused or contributed to the death of a patient (21 CFR 803)
Mandatory Problem Reporting	Health Canada (Canada)	The investigator must file a report with the Minister and notify the manufacturer (sponsor) within 72 hours of an event that comes to their attention and meets the criteria. (Health Canada: Medical Device Regulation, PART 1 and PART 3) The requirement to report an incident that occurs outside Canada does not apply unless the manufacturer has indicated, to a regulatory agency of

		the country in which the incident occurred, the manufacture's intention to take corrective action, or unless the regulatory agency has required the manufacturer to take corrective action. (Health Canada: Medical Device Regulations, Part 1; Section 59 (2))

7.8 Medtronic Adverse Event Records and Reporting Requirements

Adverse Events will be recorded and reported according to local regulatory requirements. Refer to Table 10 for Medtronic adverse event reporting requirements.

Table 10: Medtronic Adverse Event reporting

Report	Submit To	Description
Medical Device Reporting	FDA	**US and Canada:** An event about which manufacturers or importers have received or become aware of information that reasonably suggests that one of their marketed devices may have caused or contributed to a death or serious injury; or has malfunctioned and that the device or a similar device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur. (21 CFR 803)
Mandatory Problem Reporting	Health Canada	**US and Canada:** Required reporting by manufacturers concerning any incident that comes to their attention occurring inside or outside Canada and involving a device that is sold in Canada and that: a) Is related to a failure of the device or a deterioration in its effectiveness, or any inadequacy in its labeling or in its directions for use; AND b) Has led to the death or a serious deterioration in the state of health of a patient, user or other person, or could do so were it to recur. (Health Canada: Medical Device Regulation, PART 1 & PART 3)

8 RISK ANALYSIS

There are potential risks and side effects associated with participation in this study. Possible additional risks for participating in this study include the following (although others are possible):

- Radiation exposure due to potential for additional CT scan or Chest X-rays
- Electrodes used with Holter recorder might cause mild skin discomfort or irritation, or some skin discomfort following electrode removal.

8.1 Risk Minimization

Medtronic has attempted to minimize the potential risks to subjects in this study by taking the following actions:

- Selecting qualified investigators and training study personnel on the Clinical Investigation Plan.
- Requiring careful assessment of each subject prior to, during, and after the ablation procedure.
- Providing guidelines for subject selection and evaluation.
- Providing adequate instructions and labeling.
- After the ablation procedure, subjects in the clinical study will be followed at regular intervals to monitor for reoccurrence of AF and adverse events.

8.2 Potential Benefits

The Arctic Front® Cardiac CryoAblation Catheter System has been demonstrated to reduce paroxysmal atrial fibrillation in subjects, however some subjects may not receive this benefit. The information gained from this study could result in improved management of paroxysmal atrial fibrillation.

9 PLANNED STUDY CLOSURE, EARLY TERMINATION OR STUDY SUSPENSION

9.1 Planned Study Closure

Study Closure is a process initiated by distribution of an initial study closure letter. Study closure is defined as closure of a clinical study that occurs when Medtronic and/or regulatory requirements have been satisfied per the Clinical Investigational Plan and/or by a decision by Medtronic or regulatory authority, whichever occurs first. The study closure process is complete upon distribution of the Final Report or after final payments, whichever occurs last. IRB/MEC re-approvals are required until the overall study closure process is complete.

9.2 Early Termination or Suspension

Early Termination of a study is the closure of a clinical study that occurs prior to meeting all enrollment and/or follow-up visits for all enrolled subjects. This is possible for the whole study or a single center.

Study Suspension is a temporary postponement of study activities related to enrollment and distribution of the product. This is possible for the whole study or a single center.

9.3 Criteria

9.3.1 Study Termination or Suspension

Possible reasons for considering study suspension or premature termination of the study may include:

- Adverse events associated with the system or product under investigation which might endanger the safety or welfare of the subject
- Observed/suspected performance different from the product's design intent
- Decision by Medtronic or regulatory body (where the study is operating under regulatory body authority)

9.3.2 Investigator/Center Termination or Suspension

Possible reasons for clinical investigator or center termination or suspension include but are not limited to:

- Failure to obtain initial MEC/IRB/Head of Medical Institution approval or annual renewal of the study
- Consistent non-compliance to the clinical investigation plan (e.g. failure to adhere to inclusion/exclusion criteria, failure to follow subjects per scheduled follow-ups, etc.)
- Lack of enrollment
- Noncompliance to regulations and the terms of the Clinical Trial Agreement (e.g. failure to submit data in a timely manner, failure to follow-up on data queries and monitoring findings in a timely manner, etc.)
- IRB/ MEC suspension of the center
- Fraud or fraudulent misconduct is discovered (as defined by local law and regulations)
- Investigator request (e.g. no longer able to support the study)

9.4 Procedures

9.4.1 If Medtronic terminates or prematurely suspends the study:

- Medtronic will promptly inform the clinical investigators of the termination or suspension and the reasons and inform the regulatory authority (ies) (where required per regulatory requirements).
- In the case of study termination or suspension for reasons other than a temporary IRB/MEC approval lapse, the investigator will promptly inform the IRB/MEC.
- In the case of study termination, the investigator must inform the subjects and may inform the personal physician of the subjects to ensure appropriate care and follow-up is provided.
- In the case of a study suspension, subjects already enrolled should continue to be followed out of consideration of their safety, rights and welfare.

9.4.2 If the investigator terminates or suspends the study without prior agreement of Medtronic:

- The investigator will promptly inform Medtronic and provide a detailed written explanation of the termination or suspension.
- The investigator will promptly inform the institution (where required per regulatory requirements).
- The investigator will promptly inform the IRB/MEC.

9.4.3 If the IRB/MEC terminates or suspends its approval of the study:

- The investigator will promptly inform Medtronic and provide a detailed written explanation of the termination or suspension within 5 business days.
- Subject enrollment must stop until the MEC/ IRB suspension is lifted.
- Subjects already enrolled should continue to be followed in accordance with MEC/ IRB policy or its determination that an overriding safety concern or ethical issue is involved.
- The investigator will inform his/her institution (where required per local requirements).
- The investigator will promptly inform the subjects and/or the personal physician of the subjects, with the rationale for the study termination or suspension.

10 STATISTICAL METHODS AND DATA ANALYSIS

10.1 Primary Effectiveness Endpoint

The primary effectiveness endpoint is the rate of subjects free of chronic treatment failure at 36 Months. Chronic Treatment Failure is defined as:

1. Detectable AF outside of the 90 day blanked follow-up period, OR
2. The occurrence of an AF Intervention (except repeat cryoablation during the 90 day blanking period)

10.2 Primary Safety Endpoint

1. Adverse event (AE) ascertainment and reporting: AEs for all subjects will be ascertained for the full 5 year follow-up interval. All AEs will be categorized using the MedDRA or similar system, tabulated and listed in decreasing frequency order.
   a. The primary safety endpoint is the rate of subjects experiencing one or more Cryoablation Procedure Event (CPE) through 12 months. The CPE is defined as:
      i. A CPE is a device-related or procedure-related serious adverse event (SAE) with onset between the time of the subject's entry into the procedure room for the study-specified cryoablation procedure (Day 0) through the indicated onset intervals as set out in the following Table 11:

Table 11: Cryoablation Procedure Events

Cryoablation Procedure Events (CPEs):	Onset Interval
Access site complications requiring: Transfusion of 3 or more units or Surgical intervention or Permanent loss or functional impairment	Through 7 days
Cardiac damage (including MI) except for	Through 7 days
Pulmonary vein stenosis*	Through 12 months
Atrio-esophageal fistula	Through 12 months
Embolic complications (including stroke)	Through 7 days
Arrhythmias	Through 7 days
Persistent phrenic nerve palsy**	Through 12 months
Death	Through 7 days

* CPE will be assessed at the completion of the follow-up visit, as determined by CT/MRI Core Lab.
** CPE will be assessed at the completion of the follow-up as determined by chest X-ray (insp/exp)

ii. Pulmonary vein stenosis is defined as > 75% reduction in the baseline area at 12 month follow-up.
iii. Phrenic nerve palsy is defined as abnormal diaphragm excursion as demonstrated during the post-cryoablation procedure fluoroscopy.
iv. CPEs exclude
    1. adverse events that are normal and expected concomitants of catheterization and diagnostic and ablation EP procedures, such as induced arrhythmia and groin ecchymosis, but only IF that AE resolves completely AND involves only routine responses such as medication, fluids, compression, temporary pacing, or cardioversion.
    2. Atrial fibrillation or atrial flutter occurring during post-procedural hospitalization.
v. CPEs will be accrued for Retreated Subjects for the comparable 7 day period following a repeat cryoablation.

2. Primary safety endpoint: The primary safety endpoint is the rate of subjects experiencing a CPEs through 12 months.
3. Adjudication: All potential CPEs, MAFEs, device-related AEs, procedure-related AEs, SAEs and UADEs will be reviewed and adjudicated by the AEAC.

10.3 Analysis Sets

Enrolled Set: any patients who have a signed informed consent.

Intent-To-Treat Set: any enrolled subjects who meet all inclusion and exclusion criteria.

mITT (modified intent-to-treat) Set: any subjects with a Arctic Front® Cardiac CryoAblation Catheter System inserted into the vasculature for the purpose of this study.

10.4 Sample Size Justification

10.4.1 Primary Effectiveness Endpoint

Sample size was estimated using SAS V9.2 Proc Power. The sample size was calculated under an asymptotic z- test for a single binomial proportion with a continuity adjustment under the following assumptions:

- Power = 90%
- Significance level = 0.025 (one-sided)
- Assumed underlying effectiveness rate = 55%
- Performance goal = 45%

Long-term (> 12 months) effectiveness of pulmonary vein isolation for the treatment of atrial fibrillation ranges from 44-70%, with 40% reported as the minimum goal by physicians.[1] Shah et al reported that the annual rate of atrial fibrillation recurrence after one year was 8.8% and Tzou et al reported a similar annual rate of 7%.[2,3] Based on the STOP AF results and assuming an annual rate of atrial fibrillation recurrence of 7-9%, the estimated effectiveness rate at 36 months would be approximately 55%. The performance goal of 45% was determined from the lower bound of 95% CI for the primary effectiveness rate in STOP AF study.

If the underlying effectiveness rate is assumed 55%, a total of 270 evaluable subjects will be required to provide 90% power to meet this effectiveness objective.

10.4.2 Primary Safety Endpoint

Sample size was estimated using SAS V9.2 Proc Power. The sample size was calculated under an asymptotic z- test for a single binomial proportion with a continuity adjustment under the following assumptions:

- Power = 90%
- Significance level = 0.025 (one-sided)
- Assumed underlying primary safety event rate = 6%
- Performance goal = 14.8%

The performance goal 14.8% was determined on based on STOP AF study. If the underlying safety event rate is assumed 6%, a total of 141 mITT subjects will be required to provide 90% power to meet this safety objective.

10.4.3 Overall Sample Size

In order to adequately power for both the primary effectiveness and safety hypotheses, we require a sample size of 270 evaluable subjects to complete 36 months of follow-up. We estimate that the attrition rate will be approximately 10% per year for the duration of the 5 year follow-up period. Therefore the final sample size required to achieve 270 subjects followed for 36 months and account for attrition (i.e. 10% per year) is 370 mITT subjects with procedure attempts. It is expected up to 400 subjects will need to be enrolled to ensure 370 mITT subjects with procedure attempts assuming a small number of subjects who are enrolled will not undergo a procedure.

10.5 Statistical Analysis Methods

A Statistical Analysis Plan (SAP) will be developed to provide details for all planned statistical analysis. The primary analyses will be conducted when all subjects reach their required follow-up.

10.5.1 General Statistical Considerations

All analyses will be performed using SAS statistical software (SAS Institute Inc, Cary, NC). It is planned that the data from all centers that participate in this protocol will be combined for analysis.

Descriptive statistics includes but is limited to number of non-missing observations, mean, standard deviation, median, minimum, and maximum for continuous variables and count and percentage for categorical variables. Unless otherwise specified, the analysis will be performed using descriptive statistics.

10.5.2 Pooling of Study Centers for Analysis

A study center is defined as a treatment administration site or group of treatment administrative sites under the control and supervision of the same Principal Investigator. Each study center will be limited to enrolling no more than 50 subjects into the mITT set. Each center will be encouraged to enroll at least 10 subjects into the mITT set. This will prevent any single center from contributing a significant proportion of the subjects to the study. While every effort will be made to acquire similar enrollment from all participating centers, it is likely that some centers may enroll small numbers of subjects. Therefore the centers that enroll at most five subjects will be polled into a super center. The participating centers with more than five subjects enrolled will be reported individually.

10.5.3 Subject Disposition

Subject disposition (screened, analysis set allocation, discontinued along with primary reason for discontinuation) will be summarized using frequency and percent. A summary of patients enrolled by site will be provided.

10.5.4 Analysis of Baseline and Demographic Characteristics

The baseline and demographic variables of interest will be summarized using descriptive statistics. The baseline and demographic characteristics include but not limited to age, sex, race, height, weight, body mass index, medical history, comorbid conditions, cardiovascular medication history and concomitant medications. Analysis of baseline and demographic characteristics will be conducted for all analysis sets.

10.5.5 Analysis of Primary Endpoints

The study will be considered a success if both primary effectiveness and safety objectives are met at one-sided 0.025 level of significance in the final analysis. The analysis will conducted using the mITT set.

Primary Effectiveness Analysis

The following hypothesis will be tested in a one-sided test at the 0.025 significance level.

H_o: Pe $\leq$ 45%
H_a: Pe > 45%

Where Pe is the probability of chronic treatment success at 36 Months and 45% is the pre-specified performance goal based on the lower bound of 95% CI for the primary effectiveness rate in STOP AF study.

Kaplan-Meier method will be used to estimate the probability of chronic treatment success at 36 months follow-up. The standard error will be approximated using Greenwood's formula. A two-sided 95% log-log confidence interval for the probability will be constructed. The Kaplan-Meier estimate and its 95% log-log confidence interval will be constructed from the day of protocol specified ablation procedure (Day 1) through the end of follow-up. For subjects with a treatment failure, the days of follow-up will be computed as the days from Day 1 to the failure date. For subjects without failure events, days of follow-up will be computed as the days from Day 1 through the last follow-up. For subjects who are lost to follow-up, the last contact date will be used as the last follow-up date. If the lower bound of this 95% log-log confidence interval is greater than the performance goal of 45%, we can conclude the primary effectiveness objective is met.

Primary Safety Analysis

The primary safety endpoint is the occurrence of any cryoabalation procedure events (CPE) through 12 month follow-up. A CPE is a device-related or procedure-related serious adverse event (SAE) with onset between the time of the subject's entry into the procedure room for the study specified cryoablation procedure (Day 1) through the indicated follow-up intervals as set out in Table Table 11.

The parameter of interest is the probability of subjects experiencing one or more CPE through the 12 month follow-up. The following hypothesis will be tested in a one-sided test at the 0.025 significance level:

H_o: $Ps \geq 14.8\%$
H_a: $Ps < 14.8\%$

Where Ps is the probability of subjects with one or more CPE and 14.8% is the pre-specified performance goal based on the upper bound of 95% CI for the primary safety rate in the STOP AF study.

Kaplan-Meier method will be used to estimate the probability of a subject experiencing one of more CPE at 12 months follow-up. The standard error will be approximated using Greenwood's formula. A two-sided 95% log-log confidence interval for the probability will be constructed. The Kaplan-Meier estimate and its 95% log-log confidence interval will be constructed from the day of study specified cryoablation procedure (Day 1) through the end of follow-up. For subjects with safety events, the days of follow-up will be computed as the days from Day 1 to the onset date of the first safety event. For subjects without safety events, days of follow-up will be computed as the days from Day 1 through the last follow-up. For subjects who are lost to follow-up, the last contact date will be used as the last follow-up date. If the upper bound of this 95% log-log

confidence interval is less than the performance goal 14.8%, we can conclude the primary safety objective is met.

10.5.6 Analysis of Secondary Endpoints

The analyses of secondary endpoints are intended to provide additional information on the performance of Arctic Front® Cardiac CryoAblation Catheter System. All secondary analyses will be exploratory and no formal hypotheses tested.

Effectiveness Objectives

- The probability of subjects free of chronic treatment failure at the 1, 2, 4 and 5 year follow-up visits will be estimated using Kaplan-Meier method. The standard error will be approximated using Greenwood's formula. A two-sided 95% log-log confidence interval for the proportion will be constructed. This calculation will be based on the mITT Set.

Safety Objectives

a. The probability of subjects free of MAFE at the 1, 2, 3, 4 and 5 year follow-up visits will be estimated using Kaplan-Meier method. The standard error will be approximated using Greenwood's formula. A two-sided 95% log-log confidence interval for the proportion will be constructed. The analysis will be conducted in the mITT set.

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i. Major Atrial Fibrillation Event (MAFE): A MAFE is a serious adverse event (SAE) — which has not been categorized as a CPE— as set out in the following table:

Table 12: Major Atrial Fibrillation Events

Major Atrial Fibrillation Events (MAFEs):
Cardiovascular deaths
Hospitalizations for (primary reason): AF recurrence or ablation Atrial flutter ablation (excluding Type I) Systemic embolization (not stroke) Congestive heart failure Hemorrhagic event (not stroke) Antiarrhythmic drug: initiation, adjustment or complication
Myocardial infarction (MI)
Stroke

b. Long Term Safety Outcomes: Device and procedure related events, serious adverse events, unexpected adverse device effects and other safety categories will be collected through the 5 year follow-up, analyzed and reported descriptively.

Cryoablation

- Cryoablation procedure parameters such as total number of cryoablation attempts, mean number of cryoablation attempts per attempted subject and number of successful cryoablations per subject will be summarized using descriptive statistics.
- Cryoablation temperature and ablation procedure time will be summarized using descriptive statistics.

Procedure and Fluoroscopy Time

- Total procedure time defined as the period from puncture of the skin performed to obtain venous access for catheter placement to final ECG at end of procedure will be analyzed using descriptive statistics.
- Total fluoroscopy time will be analyzed using descriptive statistics.

Other

- All adverse events will be summarized by presenting the number and percentage of subjects having any AE, having an AE in each body system, and having each individual AE. Any other information collected (e.g., seriousness, severity or relatedness to device/procedure) will be presented as appropriate.

10.6 Interim Patient Safety Monitoring

No interim analysis of data for the primary endpoints is planned before the required primary safety and effectiveness follow-ups are completed.

11 DATA AND QUALITY MANAGEMENT

Data will be collected using an electronic data management system for clinical trials. CRF data will be stored in a secure, password-protected database which will be backed up nightly. Data will be reviewed using programmed and manual data checks. Data queries will be made available to centers for resolution. Study management reports may be generated to monitor data quality and study progress. At the end of the study, the data will be frozen and will be retained indefinitely by Medtronic.

Procedures in the Clinical Investigation Plan require source documentation. In some cases, items on CRFs may be considered source as long as there is evidence of the visit in the subject's record. Even when the CRF may be considered as source, an alternate method of source documentation is always strongly encouraged.

CryoConsole data from transmissions may be uploaded to secure servers. Upon receipt, this data will be maintained with databases and retrieved for analysis and reporting.

The sponsor or a regulatory authority may audit the study center to evaluate the conduct of the study. The clinical investigator(s)/institution(s) shall allow trial related monitoring, audits, Ethics Board review, and regulatory inspection(s) by providing direct access to source data/documents.

12 WARRANTY/INSURANCE INFORMATION

12.1 Warranty

Warranty information is provided in the product packaging for the Arctic Front® Cardiac CryoAblation Catheter as well as the Freezor *MAX* catheter and Cryoconsole. Additional copies are available upon request.

13 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 Clinical Investigation Plan, the Clinical Trial Agreement, and applicable regulatory requirements. Medtronic must therefore be allowed access to the subjects' case histories (clinic and hospital records, and other source data/documentation) when so requested as per the Subject Informed Consent, Privacy Authorization (US only) and Clinical Trial Agreement.

13.1 Monitoring Visits

Frequency of monitoring visits will occur based on subject enrollment, duration of the study, study compliance, findings from previous monitoring visits and any suspected inconsistency in data that requires investigation. Regulatory documents (e.g., IRB/MEC approval letters, etc.) may be reviewed at each study center. Monitoring visits will be conducted periodically to assess site study progress, the investigator's adherence to the Clinical Investigation Plan, regulatory compliance including but not limited to IRB/MEC approval and review of the study maintenance of records and reports, and review of source documents against subject CRFs. Monitors facilitate site regulatory and study compliance by identifying findings of non-compliance and communicating those findings along with

recommendations for preventative/corrective actions to site personnel. Monitors may work with study personnel to determine appropriate corrective action recommendations and to identify trends within the study or at a particular center.

14 REQUIRED RECORDS AND REPORTS

14.1 Investigator Records

The investigator is responsible for the preparation and retention of the records cited below. All of the below records, with the exception of case history records and case report forms, should be kept in the Investigator Site File (i.e., the study binder provided to the investigator) or Subject Study Binder. CRFs may be maintained and signed electronically within the electronic data capture system during the trial. The following records are subject to inspection and must be retained for a period of two years (or longer as local law or hospital administration requires) after product approval or the date on which the investigation is terminated or the date that the records are no longer required for purposes of supporting a pre-market approval application.

- All correspondence between the IRB/MEC/HOMI, sponsor, monitor, FDA and/or other regulatory bodies, and/or the investigator that pertains to the investigation, including required reports
- Subjects' case history records, including:
    - Signed and dated informed consent form
    - Observations of adverse events/adverse device effects
    - Medical history
    - Procedure and follow-up data
    - Documentation of the dates and rationale for any deviation from the protocol
    - Documentation of the dates and rationale for any deviation from the protocol
- Signed and dated CRFs
- Device Disposition Records
- All approved versions of the Clinical Investigation Plan
- Report of Prior Investigation Summary (in geographies where distributed)
- Signed and dated Clinical Trial Agreement
- Current curriculum vitae of all participating investigators
- Delegated Tasks List

- IRB/MEC approval documentation including written information that the investigator or other study staff, when member of the IRB/MEC, did not participate in the approval process
- Study training records for center staff.
- Any other records that FDA and local regulatory agencies require to be maintained.
- Final Report of the clinical investigation prepared and distributed by the sponsor
- Final investigator report prepared by center and submitted to their IRB/MEC Investigator Reports

14.2 Investigator Reports

The investigator is responsible for the preparation (review and signature) and submission to the sponsor of all case report forms, adverse events and adverse device effects (reported per the country-specific collection requirements), deaths, and any deviations from the investigation plan. If any action is taken by an IRB/MEC with respect to this clinical study, copies of all pertinent documentation must be forwarded to Medtronic in a timely manner. Reports are subject to inspection and to the retention requirements as described above for investigator records.

Investigator requirements for the reporting of safety data are listed in Section 7.

The investigator shall prepare and submit in a complete, accurate and timely manner the reports listed in this section.

Table 13: Investigator Reports for all Geographies per Medtronic requirements

Report	Submit To	Description/Constraints
Withdrawal of IRB/MEC approval	Sponsor	The investigator must report a withdrawal of approval by the reviewing IRB/MEC of the investigator's part of the investigation within 5 working days. *CFR 812.150(a)(2))*
Study Deviations	Sponsor and IRB/MEC	Any deviation from the clinical investigational plan shall be recorded together with the explanation of the deviation. Notice of deviations from the CIP to protect the life or physical well being of a subject in an emergency shall be given as soon as possible, but no later than 5 working days after the emergency occurred. Except in such emergency, prior approval is required for changes in the plan or deviations.

Final Report	IRBs/MECs Relevant Authorities	This report must be submitted within 3 months of study completion or termination.
Adverse Events		Refer to Section 7

Table 14: Investigator Reports Applicable to the United States per FDA Regulations

Report	Submit To	Description/Constraints
Withdrawal of IRB/MEC approval (either suspension or termination)	Sponsor	The investigator must report a withdrawal of approval by the reviewing IRB/MEC of the investigator's part of the investigation within 5 working days. *(21 CFR 812.150(a)(2))*
Progress report	Sponsor and IRB/MEC	The investigator must submit this report to the sponsor and IRB/MEC at regular intervals, but in no event less than yearly. *(21 CFR 812.150 (3))*.
Study deviations	Sponsor and IRB/MEC	Notice of deviations from the CIP to protect the life or physical well being of a subject in an emergency shall be given as soon as possible, but no later than 5 working days after the emergency occurred. Except in such emergency, prior approval is required for changes in the plan or deviations. If the deviation may affect the scientific soundness of the plan or the rights, safety and welfare of the subjects, the deviation must be approved by Medtronic, the IRB/MEC, and the FDA/applicable regulatory authorities. If the deviation does not affect these issues then only Medtronic must approve it. *(21 CFR 812.150(a)(4))*
Failure to obtain informed consent prior to investigational device use	Sponsor and IRBs/MECs	If an investigator uses a device without obtaining informed consent, the investigator shall report such use within 5 working days after device use. *(21 CFR 812.150(a)(5))*
Final report	Sponsor IRBs/MECs Relevant Authorities	This report must be submitted within 3 months of study completion or termination of the investigation or the investigator's part of the investigation. *(21 CFR 812.150(a)(6))*
Other	IRB/MEC and FDA	An investigator shall, upon request by a reviewing IRB/MEC, FDA or any other regulatory agency, provide accurate, complete, and current information about any aspect of the investigation. *(21 CFR 812.150(a)(7))*

14.3 Sponsor Records

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

- All correspondence which pertains to the investigation
- Investigational device traceability records
- Signed Investigator Trial Agreements, financial disclosure and current investigator curriculum vitae (signed and dated Europe only), Delegated Tasks List
- All case report forms and supporting documentation submitted by investigator, samples of consent forms, and other information provided to the subjects
- Copies of all IRB/MEC approval letters and relevant IRB/MEC correspondence
- Names of the institutions in which the clinical investigation will be conducted
- Correspondence with authorities as required by national legislation
- Forms for reporting any adverse events and adverse device effects
- ECA/MEA only: Names/contact addresses of monitors
- Statistical analyses and underlying supporting data.
- Final report of the clinical investigation
- The Clinical Investigation Plan, Investigator Brochure/Report of Prior Investigations Summary and study related reports
- Study training records for site personnel and Medtronic personnel involved in the study
- ECA/MEA only: Insurance certificates
- Any other records that local regulatory agencies require to be maintained

14.4 Sponsor Reports

Medtronic shall prepare and submit the following complete, accurate, and timely reports listed in the tables below (by geography). In addition to the reports listed below, Medtronic shall, upon request of reviewing IRB/MEC, regulatory agency or FDA, provide accurate, complete and current information about any aspect of the investigation.

Safety data Medtronic reporting requirements are listed in Section 7.8.

Medtronic records and reports will be stored in locked file cabinets at Medtronic during the course of the study. Electronic versions of the reports will be kept on a password-protected document management system. After closure of the study, all records and reports will be archived indefinitely.

Table 15: Sponsor Reports for Canada

Report	Submit To	Description
Premature termination or suspension of the clinical investigation	Investigators IRB/MEC Relevant authorities Head of the Institution	Provide prompt notification of termination or suspension and reason(s). *(ISO 14155-1:2003(E)(k))*
Investigator List	FDA	Submit at 6-month intervals, a current list of the names and addresses of all investigators participating in the investigation. *(21 CFR 812.150(b)(4))*
Recall and device disposition	Investigators Head of Institution IRB/MEC relevant authorities FDA	Notification within 30 working days and will include the reasons for any request that an investigator return, repair, or otherwise dispose of any devices. *(21 CFR 812.150(b)(6))*
Study deviation	Investigators	Ensure that all deviations from the Clinical Investigation Plan are reviewed with the appropriate clinical investigator(s), are reported on the case report forms and the final report of the clinical investigation. *(ISO 14155-1:2003(E)(h))* Site specific study deviations will be submitted to investigators quarterly.

Table 16: Sponsor Reports for the United States

Report	Submit To	Description
Premature termination or suspension of the clinical investigation	Investigators IRB/MEC Relevant authorities Head of the Institution	Provide prompt notification of termination or suspension and reason(s). *(ISO 14155-1:2003(E)(k)), (MHLW Ordinance 36, Article 32)*
Withdrawal of IRB/MEC approval	Investigators, IRB/MEC, FDA, and relevant authorities	Notification within five working days. *(21 CFR 812.150(b)(2))*
Withdrawal of FDA approval	Investigators, IRB/MEC, and relevant authorities	Notification within five working days. *(21 CFR 812.150(b)(3))*
Investigator List	FDA	Submit at 6-month intervals, a current list of the names and addresses of all investigators participating in the investigation. *(21 CFR 812.150(b)(4))*
Progress Reports	IRB/MEC FDA	Progress reports will be submitted at least annually. *(21 CFR 812.150(b)(4)(5), 812.36(f)*
Recall and device disposition	Investigators Head of Institution IRB/MEC relevant authorities FDA	Notification within 30 working days and will include the reasons for any request that an investigator return, repair, or otherwise dispose of any devices. *(21 CFR 812.150(b)(6))*
Failure to obtain informed consent	FDA	Investigator's report will be submitted to FDA within five working days of notification. *(21 CFR 812.150(b)(8))*
Final report	Investigators, IRB/MEC, Regulatory authorities upon request, and FDA	Medtronic will notify FDA within 30 working days of the completion or termination of the investigation. A final report will be submitted to the FDA, investigators, and IRBs/MECs within six months after completion or termination of this study. *(21 CFR 812.150(b)(7))*
Study deviation	Investigators	Ensure that all deviations from the Clinical Investigation Plan are reviewed with the appropriate clinical investigator(s), are reported on the case report forms and the final report of the clinical investigation. *(ISO 14155-1:2003(E)(h))* Site specific study deviations will be submitted to investigators quarterly.

Table 17: Study Milestones/Timeline

Milestone	Timeline
Estimated date of study initiation	November 2011
Estimated monthly number of study sites with IRB approval	4-5*
Estimated number of subjects enrolled per month	35**
Estimated date of enrollment completion	March 2013
Estimated date of study follow-up completion	March 2018
Estimated date for Final Report submission	June 2018

* Number of sites to obtain IRB approval per month during study initiation
** This enrollment rate assumes all sites are approved to enroll.

Appendix A: Protocol Acronyms and Abbreviations

AE	adverse event
AF	atrial fibrillation
AFD	atrial fibrillation drug
APS	acute procedural success
CPE	cryoablation procedure event
CRF	case report form
CT	computed tomography
CTF	chronic treatment failure
ECG	electrocardiogram
EP	electrophysiology
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
IDE	Investigational Device Exemption
INR	international normalized ratio
IRB	Institutional Review Board
IVC	inferior vena cava
LA	left atrium or left atrial
MAFE	major atrial fibrillation event
MRI	magnetic resonance imaging
NYHA	New York Heart Association
PAF	paroxysmal atrial fibrillation
PPM	permanent pacemaker
PV	pulmonary vein
RA	right atrium
RF	radiofrequency
TEE	trans-esophageal echocardiography
TIA	transient ischemic attack
TTE	trans-thoracic echocardiography

SAE serious adverse event

SVC superior vena cava

UADE unanticipated adverse device effect

U.S. United States

Appendix B: Summary of STOP AF PAS Protocol Changes

Sponsor	Approved, Ver 4 18-Aug-2011
FDA	Not approved, 20-Jun-2011
Prior	Ver 3, 20-Jun-2011
Section 1	Section 1.2 Added proportion of total study enrollments required to come from new Arctic Front user investigational sites
Section 2	No change
Section 3	No change
Section 4	Section 4.5 Language updated to clarify the number of new Arctic Front user investigational sites to be included in the STOP AF PAS and added site selection criteria.
Section 5	No change
Section 6	No change
Section 7	No change
Section 8	No change
Section 9	No change
Section 10	No change
Section 11	No change
Section 12	No change
Section 13	No change
Section 14	No change
Appendix A	No change
Appendix B	Updated for changes made from Ver 3 to Ver 4.

[1] Katritsis D, Wood M, Giazitzoglou E, Shepard R, Kourlaba G, Ellenbogen K. Long-term follow-up after radiofrequency catheter ablation for atrial fibrillation. Europace. 2008;10:419-424.
[2] Shah A, Mittal S, Sichrovsky T, Cotiga D, Arshad A, Maleki K, Pierce W, Steinberg J. Long-term outcome following successful pulmonary vein isolation: pattern and prediction of very late recurrence. J Caridiovasc Electrophysiol. 2008;19:661-667.
[3] Tzou W, Marchlinski F, Zado E, Lin D, Dixit S, Callans D, Cooper J, Bala R, Garcia F, Hutchinson M, Riley M, Verdino R, Gerstenfeld E. Long-term outcome after successful catheter ablation of atrial fibrillation. Circ Arrhythm Electrophysiol. 2010;3:237-242.