Medtronic

Clinical Investigation Plan

Clinical Investigation Plan/Study Title	ArcticLine Feasibility Study
Clinical Investigation Plan Identifier	MDT16015
Study Product Name	ArcticLine™ Cardiac Cryoablation Catheter
Sponsor/Local Sponsor	**United States** Medtronic, Inc. 8200 Coral Sea Street NE Mounds View, MN U.S.A. 55112 1-800-328-2518 **Canada** Medtronic of Canada 99 Hereford Street Brampton, Ontario, L6Y 0R3 +1-905-460-3800
Document Version	Version 1.0, 14JUN2017
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Confidentiality Statement

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Sponsor Contact Information

Medtronic contact information is provided in Table 1. 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 as needed.

Table 1: Study Sponsor and Monitoring Contact Information

Study sponsors and contacts
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1. Glossary

Term	Definition
AE	Adverse event
AF	Atrial fibrillation
AAD	Antiarrhythmic drug
ACT	Activated clotting time
ADE	Adverse device effect
AFL	Atrial flutter
AHA	America Heart Association
AT	Atrial tachycardia
C	Celsius
CV	Curriculum vitae
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CIP	Clinical investigation plan
CRF	Case report form
CTA	Clinical trial agreement
CTI	Cavotricuspid isthmus
DD	Device deficiency
e.g.	For example,
ECG	Electrocardiogram
FD	Financial disclosure
FAL	Foreseeable adverse event list
FDA	Food and Drug Administration
GCP	Good clinical practice
ID	Identification
IC	Informed consent
IDE	Investigational device exemption
IFU	Instructions For Use
IRB	Institutional review board
ISO	International Organization for Standardization
ICMJE	International Committee of Medical Journal Editors
LAD	Left atrial diameter

Term	Definition
LVEF	Left ventricular ejection fraction
MDD	Medical Device Directive
MEC	Medical ethics committee
MedDRA	Medical Dictionary for Regulatory Activities
MI	Mitral isthmus
NOAC	Novel oral anticoagulant
NYHA	New York Heart Association
N_2O	Nitrous Oxide
PAF	Paroxysmal atrial fibrillation
PV	Pulmonary vein
PVI	Pulmonary vein isolation
REB	Research Ethics Board
RF	Radiofrequency
RI	Right inferior
RS	Right superior
SAE	Serious adverse event
SAP	Statistical analysis plan
SADE	Serious adverse device effect
TEE	Transesophageal echocardiogram
TIA	Transient ischemic attack
TTE	Transthoracic echocardiogram
US	United States
UADE	Unanticipated adverse device effect
USADE	Unanticipated serious adverse device effect

2. Synopsis

Title	ArcticLine Feasibility Study ("Study")
Clinical Study Type	Feasibility
Product Name	ArcticLine Cardiac Cryoablation Catheter ("ArcticLine Catheter")
Sponsor	**United States** Medtronic, Inc. 8200 Coral Sea Street NE Mounds View, MN U.S.A. 55112 1-800-328-2518
Local Sponsor	**Canada** Medtronic of Canada 99 Hereford Street Brampton, Ontario, L6Y 0R3 Canada +1-905-460-3800
Indication under investigation	The proposed indication for the ArcticLine Catheter evaluated in this Study is as follows: The ArcticLine Cardiac Cryoablation Catheter is indicated for creating endocardial linear lesions, subsequent to successful pulmonary vein isolation, during cardiac ablation procedures for treatment of patients with persistent atrial fibrillation. The ArcticLine Catheter can also be used to treat typical atrial flutter.
Investigation Purpose	Collect preliminary safety and effectiveness data on the ArcticLine Catheter
Product Status	

Component	Model Number	Geography
ArcticLine™ Cardiac Cryoablation Catheter	2AL35	Canada (investigational) US (investigational)
CryoConsole™, including Accessories	106A3, Models 10000-008-04 or 10000-008-08	Canada (commercial) US (commercial)
ArcticLine™ Catheter File	Not applicable	Canada (investigational) US (investigational)
FlexCath® Advance Steerable Sheath 12 Fr	4FC12	Canada (investigational) US (investigational)
Arctic Front Advance® Cardiac Cryoablation Catheter	2AF233	Canada (commercial)
	2AF283	Canada (commercial)
	2AF234	US (investigational)
	2AF284	US (investigational)

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<tr><td></td><td>
<table>
<tr><th>Component</th><th>Model Number</th><th>Geography</th></tr>
<tr><td rowspan="4">Freezor® MAX Cardiac Cryoablation Catheter</td><td>209F3</td><td>Canada (commercial)</td></tr>
<tr><td>209F5</td><td>Canada (commercial)</td></tr>
<tr><td>239F3</td><td>US (investigational)</td></tr>
<tr><td>239F5</td><td>US (investigational)</td></tr>
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</td></tr>
<tr><td>Primary Objective(s)</td><td>Estimate the incidence of ArcticLine Catheter-related and ArcticLine cryoablation procedure-related serious adverse events (SAEs) with an onset date within 7 days post-procedure</td></tr>
<tr><td>Ancillary Objective(s)</td><td>There are seven (7) ancillary objectives for the study, as follows:
1. Estimate the percentage of patients with acute treatment success of the ArcticLine Catheter at the left atrial roof and posterior wall in patients with demonstrated entrance block of all pulmonary veins and who underwent roof and posterior wall ablation with ArcticLine.
2. Estimate the percentage of patients with acute treatment success of the ArcticLine Catheter at the mitral isthmus in patients who underwent mitral isthmus ablation with ArcticLine.
3. Estimate the percentage of patients with acute treatment success of the ArcticLine Catheter at the CTI in patients who underwent CTI ablation with ArcticLine.
4. Characterize chronic treatment success of the ArcticLine Catheter in patients with demonstrated entrance block of all pulmonary veins.
5. Estimate the incidence of ArcticLine Catheter-related and ArcticLine cryoablation procedure-related serious adverse events (SAE) through the 12 month visit.
6. Characterize procedural data (e.g. procedure time, fluoroscopy time, fluoroscopy dose, number of applications, left atrial dwell time)
7. Estimate the incidence of adverse events through the 12 month visit that meet the following, as defined in the Clinical Investigation Plan:
• Atrioesophageal fistula
• Cardiac perforation/tamponade
• Cerebrovascular accident
• Coronary artery spasm
• Death
• Esophageal injury
• Lung injury (including hemoptysis)
• Major bleeding
• Myocardial infarction
• Pericarditis
• Phrenic nerve injury (ongoing from hospital discharge)
• Pulmonary vein stenosis
• Symptomatic persistent iatrogenic atrial septal defect</td></tr>
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	• Transient ischemic attack • Vagal nerve injury • Vascular access complications
Study Design	The study is a prospective, interventional, multi-center, non-randomized, single arm, unblinded clinical study. Adult subjects with history of persistent atrial fibrillation (AF), including those with concomitant typical atrial flutter (AFL), to undergo ablation of: • Pulmonary veins (required, unless prior successful pulmonary vein isolation confirmed at start of study procedure), • Left atrial roof and posterior wall (required) • Mitral isthmus (optional, as determined by investigator), and • Cavo-tricuspid isthmus (required if subject has a history of AFL or AFL is induced during the study procedure, otherwise optional as determined by investigator). Study subjects from all participating geographies will be followed for 12 months after the index ArcticLine procedure and will be exited from the study at the conclusion of the 12 month follow-up visit.
Sample Size	Up to 30 subjects will be treated with the ArcticLine Catheter

Inclusion/ Exclusion Criteria	<u>Inclusion Criteria</u>
	• Symptomatic persistent AF, defined as continuous AF that is sustained beyond 7 days and documented via consecutive ECG recordings
	• Age 18 through 80 years old
	• Failure or intolerance of at least one Class I or III antiarrhythmic drug
	• Subject is able and willing to consent to participate in the study and will commit to completion of all follow-up requirements
	
	<u>Exclusion Criteria</u>
	• Longstanding persistent AF, defined as continuous AF greater than12 month duration
	• Left atrial diameter greater than 5.0 cm
	• Active systemic infection
	• History of thromboembolic event within the past 6 months or evidence of intracardiac thrombus at the time of the procedure
	• Prior left atrial ablation attempt, with exception of:
	  ○ Any pulmonary vein isolation attempt to treat AF, or
	  ○ Successful ablation to treat Wolff-Parkinson White syndrome
	• History of left atrial tachycardia

	• History of cardiac ablation within 90 days of planned clinical study procedure
	• Planned concomitant ventricular ablation[1]
	• Cryoglobulinemia
	• Structural heart disease of clinical significance including:
	  ○ NYHA Class IV Heart Failure
	  ○ Diagnosed with NYHA Class III Heart Failure for more than six months at time of the study ablation procedure
	  ○ LVEF less than 35%
	  ○ Any cardiac surgery (e.g. CABG) within 3 months of the ablation procedure
	  ○ Any mechanical heart valve, prior aortic or tricuspid valve replacement (e.g. valvotomy, valve replacement) or tricuspid valve repair
	  ○ Severe mitral valve regurgitation or stenosis
	  ○ Significant congenital anomaly or anatomy unable to accommodate device
	• Prior surgical maze procedure
	• Unstable angina
	• Myocardial infarction within 3 months of the ablation procedure
	• Presence of primum or secundum atrial septal defect
	• Anomalous pulmonary venous return
	• Prior surgery for congenital heart disease including atrial septal defect repair
	• Hypertrophic cardiomyopathy with LV septal wall thickness >1.5 cm
	• Uncontrolled hyperthyroidism
	• Thrombocytosis, thrombocytopenia (including history of heparin-induced thrombocytopenia)
	• Severe comorbidity or poor general physical/mental health that, in the opinion of the investigator, will not allow the subject to be a good study candidate
	• History of blood clotting or bleeding abnormalities
	• Contraindication to all anticoagulation (e.g. novel oral anticoagulants, heparin or warfarin)
	• Pregnant, nursing or planning to become pregnant during study duration
	• Enrollment in another clinical trial without prior approval from Medtronic
	• Presence or use of left atrial appendage closure device

[1] Concomitant ventricular ablation will be allowed in the proposed feasibility clinical study if determined to be in the best interest of the subject at the time of the procedure as assessed by the Investigator. However, the ArcticLine Catheter may not be used for these purposes.

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- Presence of or planned implantation of a pacemaker, implantable cardiac defibrillator, implantable loop recorder or cardiac resynchronization device with permanent lead placement
- Pre-existing hemidiaphragmatic paralysis
- Life expectancy less than one year
- Known drug or alcohol dependency
- Existing pulmonary vein stent(s)

</td></tr>
<tr><td>Study Procedures and Assessments</td><td>

	Baseline	Procedure	Pre-Discharge	1 week[1]	3 month[2]	6 month[2]	12 month[2]	Unscheduled	Repeat Ablation after Blanking
Informed Consent	X								
Inclusion/Exclusion Criteria	X								
Medical History	X								
Physical Exam	X								
AAD & Anticoagulation Medication Review	X		X	X	X	X	X	X	
Pregnancy Screen[3]	X								
Arrhythmia Symptom Review	X			X	X	X	X	X	
Transthoracic Echocardiogram (TTE)[4]	X								
Transesophageal Echocardiogram (TEE)	X								
12 Lead ECG	X		X		X	X	X	X	
Procedure Information		X							X

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		Baseline	Procedure	Pre-Discharge	1 week[1]	3 month[2]	6 month[2]	12 month[2]	Unscheduled	Repeat Ablation after Blanking
	24h Continuous Monitoring with Holter						X	X		
	Patient Activated Ambulatory ECG Monitor					Monthly and symptomatic episodes				
	Adverse Events	As they occur								
	Device Deficiencies	As they occur								
	Study Deviations	As they occur								
	Notes: *[1]Phone visit and/or office visit with Nurse Coordinator* *[2]Office visit* *[3]Female subjects of child bearing potential only* *[4] Only required if data not available from within 6 months prior to consent date*									
Safety Assessments	Clinical Events Committee: An independent committee comprised of electrophysiologists not participating in the study will review and adjudicate all adverse events as well as all deaths for subjects participating in the study.									
Statistics	No formal hypotheses for this study: • Data will be reported as collected and no imputation will be performed for missing or incomplete observations. • Analyses are planned at the following time points: o After completion of the first 10 subject index procedures and 1 week follow-up visit o After completion of all 30 subject index procedures and 1 week follow-up visit o After completion of all subject follow-up visits through 12 month follow-up visit									

3. Introduction

3.1. Background

Atrial fibrillation (AF) is a common and disabling cardiac arrhythmia with a heterogeneous clinical presentation. The fundamental pathophysiology consists of atrial wavelets propagating in different directions, causing disorganized atrial depolarizations without effective atrial contraction, with concomitant rapid and irregular ventricular contractions. As published in the 2017 HRS/EHRA/ECAS/APHRS/SOLAECE Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation, there are several classifications for AF: paroxysmal AF (PAF) is defined as AF that terminates spontaneously or with intervention within 7 days of onset; persistent AF is defined as continuous AF that is sustained beyond 7 days; and long-standing persistent AF is defined as continuous AF of greater than 12-month duration.[2]

AF is the most common of the sustained arrhythmias affecting millions of people worldwide. In the US, AF affects between 2.7 million and 6.1 million adults[3], and that number is expected to double over the next 25 years.[4] Prolonged AF may lead to electrical, mechanical, and structural changes to the left atrium, which may then progress to tachycardia-induced cardiomyopathy, heart failure and/or persistent AF. Persistent AF represents approximately 25% of AF cases.[5] The prognosis is related to the underlying cause of the disease, with idiopathic causes having the best prognosis and ischemic cardiomyopathy having a poor prognosis. The mortality rate in patients with AF is twice that of patients without AF, and the risk of AF-related stroke is 5-fold compared to the risk in patients without AF.[6] In comparison to patients with PAF, patients with persistent AF are at a

[2] Calkins H, et al., 2017 HRS/EHRA/ECAS/APHRS/SOLAECE Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation, Heart Rhythm (2017), doi:10.10106/j.hrthm.2017.05.012.

[3] January C, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2014.

[4] Go A, et al. Prevalence of Diagnosed Atrial Fibrillation in Adults: National Implications for Rhythm Management and Stroke Prevention: the AnTicoagulation and Risk Factors In Atrial Fibrillation (ATRIA) Study. JAMA. 2001; 285(18): 2370-2375.

[5] Zoni-Berisso M, et al. Epidemiology of atrial fibrillation: European perspective. Clinical Epidemiology. 2014;6:213-220. doi:10.2147/CLEP.S47385.

[6] Wolf P, et al. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke. 1991;22(8):983-988.

significantly greater risk for cardiac mortality (hazard ratio [HR], 2.37; 95% confidence interval [CI], 1.19-4.73) and all-cause mortality (HR, 1.89; CI, 1.30-2.74).[7]

In the US, approved treatment options for patients with persistent AF are presently limited to pharmaceutical therapy and concomitant surgical ablation, which are unsatisfactory for many patients with AF. Per the 2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation, "Antiarrhythmic drug (AAD) efficacy is modest and asymptomatic AF recurrences are common".[3] All AADs may result in adverse events requiring therapy discontinuation and, with the exceptions of amiodarone and propafenone, increase the likelihood of proarrhythmia.[2] Side effects for AADs include bradycardia, palpitations, fatigue, dizziness, nausea and vomiting, stomach pain, constipation and diarrhea, rash, vision problems, and urinary retention. However, there is a growing body of evidence supporting catheter ablation as a reasonable option for treating persistent AF patients. In 2017, the HRS/EHRA/ECAS/APHRS/SOLAECE Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation continued the Class IIa Level B recommendation (as previously published in the 2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation[8]) for catheter and surgical ablation of AF for persistent symptomatic AF (refractory or intolerant to at least one Class I or III AAD), stating "the benefits of an AF ablation procedure exceed the risks, and that it is reasonable to perform AF ablation".[2] In the previously published 2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation, the level of evidence supporting the recommendation moved to Class IIa, Level A.[2] The current challenge for those who treat this patient cohort is the determination of which additional lesions sets can be performed safely with the highest efficacy in patients and whether or not the technology used has an impact on the results.

Catheter ablation treatment strategies for AF have evolved over time and currently include pulmonary vein isolation (PVI) as a cornerstone of ablation therapy in all types of AF (paroxysmal and persistent).[9, 10] AF arises primarily from the left side of the heart in the atrium, particularly where the pulmonary veins (PVs) join the atrium. The fundamental basis for the AF ablation procedure is the elimination of initiating triggers and the creation of myocardial lesions that block

[7] Ghanbari H, et al. Mortality and cerebrovascular events after radiofrequency catheter ablation of atrial fibrillation. Heart Rhythm. 2014;11:1503-1511.

[8] Calkins H, et al. 2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: Recommendations for Patient Selection, Procedural Techniques, Patient Management and Follow-up, Definitions, Endpoints, and Research Trial Design. Heart Rhythm 2012;9:632-696.

[9] Raviele, et al. Venice Chart International consensus Document on Atrial Fibrillation: 2011 Update. J Cardiovasc Electrophysiol, 2012;23:890-923.

[10] Jais P, et al. Stepwise Catheter Ablation of Chronic Atrial Fibrillation: Importance of Discrete Anatomic Sites for Termination. *J Cardiovasc Electrophysiol*. 2006;17: S28-S36, Suppl. 3.

the propagation of AF wave fronts from the triggering source. The muscular sleeves both within and near the PVs have been established as a critical source of AF triggers.[11]

Over the past decade, there have been many different ablation strategies that have been developed and applied to the treatment of persistent AF, including: complex fractionated atrial electrograms (CFAE), ganglionated plexi, rotors and linear ablation. One such strategy, the stepwise approach was introduced over 10 years ago.[8,12] The stepwise strategy assumed that better outcomes were obtained when AF was organized and then broke due to additional ablation and substrate modification. The strategy was observational in nature and presumed better outcomes with a stepwise series of radiofrequency (RF) ablations. However, more recently the stepwise strategy has been the topic of reevaluation as outcomes may have been more biased by patient cohorts rather than ablation strategy.[13]

The largest randomized control trial to-date looking at outcomes of catheter ablation in the persistent AF population, STAR AF II[14], demonstrated no significant difference in freedom from AF or AF/atrial flutter/atrial tachycardia across three study arms (PVI vs. PVI + complex fractionated electrograms vs. PVI + lines). It is important to note that one of the trial conclusions was the statement that "...reason for the lack of benefit associated with additional ablation in our trial is unclear". The question is open as to whether the use of RF ablation technology in the STAR AF II trial had an impact on the ability to achieve transmural and contiguous lesions. While an important trial in this space, STAR AF II has not definitively answered the question of whether or not lines are effective. Subsequently, Kirchhof and Calkins published a clinical update on catheter ablation in patients with persistent atrial fibrillation, stating: "better technology is needed to achieve transmural lesions. This has implications not only for the evaluation of linear lesions but also for other ablation concepts". [15]

Medtronic proposes there is a need to investigate the utility of lines using technology (i.e. ArcticLine Catheter) capable of creating contiguous, transmural, and durable lesions with fewer applications. ArcticLine is expected to be a safe and effective alternative to the current technology

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[11] Calkins H, et al. HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: Recommendations for personnel, Policy, Procedures and Follow-Up. *Europace*. 2007;9(6):335-379.

[12] Rostock T, et al. Chronic Atrial Fibrillation Is a Biatrial Arrhythmia Data from Catheter Ablation of Chronic Atrial Fibrillation Aiming Arrhythmia Termination Using a Sequential Ablation Approach. *Circ Arrhythmia Electrophysiol.* 2008;1:344-353.

[13] Winkle RA. How much ablation to eliminate atrial fibrillation: Is less more or is more more? *Heart Rhythm*. Epub ahead of print. DOI: http://dx.doi.org/10.1016/j.hrthm.2015.06.031

[14] Verma A, et al. Approaches to catheter ablation for persistent atrial fibrillation. N Engl J Med 2015; 372:1812-1822.

[15] Kirchof and Calkins. Catheter ablation in patients with persistent atrial fibrillation. European Heart J. doi:10.1093/eurheartj/ehw260.

used to achieve linear ablation (i.e. RF ablation). RF ablation uses a point-by-point approach, requiring multiple catheter applications which can leave gaps. We anticipate the safe use of ArcticLine in this feasibility study will contribute to planning future clinical evidence activities that support the premise that linear ablation can be safe and effective when created with the ArcticLine Catheter.

In regards to patients with a history of cavotricuspid isthmus-dependent flutter, or inducible CTI-dependent atrial flutter at the time of the ablation procedure, the 2017 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation[2] published a Class I Level B recommendation for ablation, stating it "can be performed safely, easily, and with only a slight prolongation in procedure time". As the clinical evidence is already strong to support the success of CTI ablation to treat typical atrial flutter, Medtronic anticipates that the ArcticLine Catheter can be used safely to successfully treat typical atrial flutter with the added benefit of requiring fewer applications.

3.2. Purpose

The purpose of the study is to collect preliminary safety and effectiveness data on the ArcticLine Catheter when used to treat persistent AF and right atrial cavotricuspid isthmus dependent atrial flutter ("typical atrial flutter"). These data will be used to guide subsequent product development activities for the ArcticLine Catheter, including feedback on device design and input into a future pivotal study.

4. Objectives and Endpoints

4.1. Objectives

4.1.1. Primary Objective(s)

Estimate the incidence of ArcticLine Catheter-related and ArcticLine cryoablation procedure-related serious adverse events (SAEs) with an onset date within 7 days post-procedure.

Primary Endpoint

ArcticLine Catheter-related or ArcticLine cryoablation procedure-related SAEs, with an onset date within 7 days post-procedure, as adjudicated by the Clinical Events Committee (CEC), described as follows:

- Atrioesophageal fistula
- Cardiac perforation/tamponade
- Cerebrovascular accident
- Death
- Esophageal injury
- Major bleeding
- Myocardial infarction
- Pericarditis
- Phrenic nerve injury (ongoing at hospital discharge)
- Transient ischemic attack
- Vagal nerve injury resulting in esophageal dysmotility or gastroparesis
- Vascular access complications

4.1.2. Ancillary Objective #1

Estimate the percentage of patients with acute treatment success of the ArcticLine Catheter at the left atrial roof and posterior wall in patients with demonstrated entrance block of all pulmonary veins and who underwent roof and posterior wall ablation with ArcticLine.

Ancillary Endpoint #1

Subjects must have confirmed block at the roof line and posterior wall line via periprocedural assessment of posterior wall isolation at the completion of the cryoablation procedure to be considered an acute treatment success.

4.1.3. Ancillary Objective #2

Estimate the percentage of patients with acute treatment success of the ArcticLine Catheter at the mitral isthmus in patients who underwent mitral isthmus ablation with ArcticLine.

Ancillary Endpoint #2

Subjects must have confirmed bi-directional conduction block at the mitral isthmus line via periprocedural assessment at the completion of the cryoablation procedure to be considered an acute treatment success.

4.1.4. Ancillary Objective #3

Estimate the percentage of patients with acute treatment success of the ArcticLine Catheter at the CTI in patients who underwent CTI ablation with ArcticLine.

Ancillary Endpoint #3

Subjects must have confirmed bi-directional conduction block at the CTI line via periprocedural assessment at the completion of the cryoablation procedure to be considered an acute treatment success.

4.1.5. Ancillary Objective #4

Characterize chronic treatment success of the ArcticLine Catheter in patients with demonstrated entrance block of all pulmonary veins.

Ancillary Endpoint #4

AF/AFL/AT episodes of at least 30 seconds duration from the end of the 90 day blanking period through the 12 month visit.

4.1.6. Ancillary Objective #5

Estimate the incidence of ArcticLine Catheter-related and ArcticLine cryoablation procedure-related serious adverse events (SAE) through the 12 month visit.

Ancillary Endpoint #5

ArcticLine Catheter-related or ArcticLine cryoablation procedure-related SAEs, as adjudicated by the Clinical Events Committee (CEC).

4.1.7. Ancillary Objective #6

Characterize procedural data:

- Total procedure time
- Total ArcticLine Catheter use time
- Left atrial dwell time
- Total fluoroscopy time
- Total fluoroscopy time during ArcticLine Catheter use
- Application duration
- Number of applications
- Fluoroscopy dose

Ancillary Endpoint #6

- Total procedure time is defined as time from first venous access to time of last catheter removal.
- Total ArcticLine Catheter use time is defined as cumulative time from each introduction of ArcticLine Catheter into the body to its removal.
- Left atrial dwell time is defined as time from transseptal puncture to time of removal of last sheath/catheter from the left atrium.
- Total fluoroscopy time is defined as total fluoroscopy time used during the procedure.
- Total fluoroscopy time during ArcticLine Catheter use is defined as the cumulative fluoroscopy time from each introduction of ArcticLine Catheter into the body to its removal.
- Application duration is defined as total duration in which cryoablation from the ArcticLine Catheter is applied to cardiac tissue overall and individually to each target area.
- Number of applications is defined as the total number of times in which the ArcticLine Catheter was used to ablate cardiac tissue overall and individually to each target area.
- Total fluoroscopy dose is defined as the amount of radiation deposited into the tissue, measured in Gy or mGy units.

4.1.8. Ancillary Objective #7

Estimate the incidence of adverse events (AEs) through the 12 month visit.

Ancillary Endpoint #7

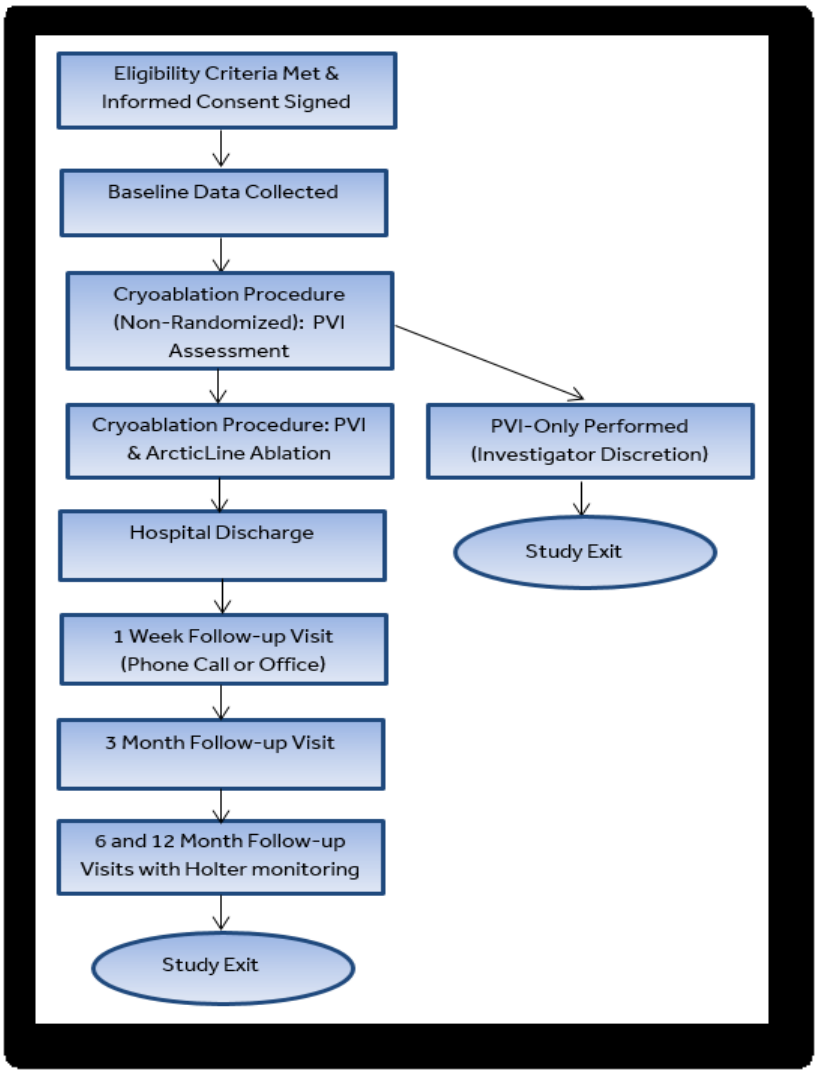
Characterize adverse events through the 12 month visit, described as follows:

- Atrioesophageal fistula
- Cardiac perforation/tamponade
- Cerebrovascular accident
- Coronary artery spasm
- Death
- Esophageal injury
- Lung injury (including hemoptysis)
- Major bleeding
- Myocardial infarction
- Pericarditis
- Phrenic nerve injury (ongoing from hospital discharge)
- Pulmonary vein stenosis
- Symptomatic persistent iatrogenic atrial septal defect
- Transient ischemic attack
- Vagal nerve injury
- Vascular access complications

5. Study Design

Medtronic is sponsoring the ArcticLine Feasibility Study: a prospective, interventional, multi-center, non-randomized, single arm, unblinded clinical study. The goal of the study is to collect preliminary safety and effectiveness data on the ArcticLine Catheter. The study design diagram is shown in Figure 1. Up to 45 subjects will be enrolled in up to 4 centers in the United States and Canada with up to 30 of these subjects treated with the ArcticLine Catheter. It is anticipated that at least 30 ArcticLine Catheters will be used in this study to ensure the sample size is met. The maximum number of subjects that may be treated at a single center is 15 subjects (50% of the total treated).

Figure 1: Study Design Flowchart



5.1. Duration

Subjects from all participating geographies will be followed for 12 months after the index ArcticLine ablation procedure and then be exited from the study. Accordingly, the expected total study duration is approximately 21 months, representing 9 months of enrollment and 12 months of subject follow-up. Subjects will not be replaced with newly enrolled subjects upon early study exit.

5.2. Rationale

The study has been designed to collect preliminary safety and effectiveness data of the ArcticLine Catheter. Due to the feasibility nature of the study, a comparator arm is not included. There is currently no catheter on the market in either Canada or the United States that is capable of creating a linear lesion with a single application.

A traditional feasibility study with a primary safety objective was chosen for the following reasons:

- The current standard for creating a linear lesion is to use a point-by-point approach with a focal catheter and stitch lesions together. This technique has produced mixed clinical evidence regarding effectiveness. This study investigates the safety and performance of a catheter specifically designed to make linear lesions.
- Data from the study will be used to guide subsequent product development activities for the ArcticLine Catheter, including a potential future pivotal study.

5.3. Minimization of Bias

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

- Subjects will undergo screening to confirm eligibility for enrollment with defined inclusion/exclusion criteria prior to enrollment.
- Subject demographics will be collected at baseline to later assess possible characteristics that may influence endpoints.
- All centers and geographies will use the same version of the CIP and case report forms.
- All investigational center personnel and Medtronic personnel will be trained on their respective aspects of the study using standardized training materials.
- All investigational center personnel will be trained on and required to follow the CIP.
- An independent Clinical Events Committee (CEC) will be utilized to review and adjudicate reported adverse events and deaths.
- An independent core lab will be utilized to review and adjudicate the arrhythmia component of the ancillary objectives.

- A statistical analysis plan (SAP) will be developed prior to analyzing data. The plan will document all pre-specified analyses and analysis methods.
- Monitoring will be conducted to review adherence to the CIP and perform source data verification per the Monitoring Plan.
- A maximum of 15 treated subjects will be allowed at a single investigational center to ensure an even distribution of total subjects across centers.

In summary, potential sources of bias that may be encountered in this clinical study have been considered and minimized by thorough, careful study design.

6. Product Description

6.1. General

Information on the components included in the study are listed in Table 2 and described below. Instructions For Use (IFU) of the devices used in the study are provided in their respective manuals.

There are no changes to the market-released FlexCath Advance Steerable Sheath ("sheath"), CryoConsole, including accessories (with exception of catheter software file), Arctic Front Advance Cardiac Cryoablation Catheter, or Freezor MAX Cardiac Cryoablation Catheter devices planned at this time.

Table 2: Device Information

Component	Required Use in Study?	Model Number	Geography	Manufacturer
ArcticLine™ Cardiac Cryoablation Catheter	Yes	2AL35	Canada (investigational) US (investigational)	Medtronic CryoCath LP
CryoConsole™, including Accessories	Yes	106A3, Models 10000-008-04 or 10000-008-08	Canada (commercial) US (commercial)	
ArcticLine™ Catheter File	Yes	Not applicable	Canada (investigational) US (investigational)	
FlexCath Advance® Steerable Sheath 12 Fr	Yes	4FC12	Canada (investigational) US (investigational)	
Arctic Front Advance® Cardiac Cryoablation Catheter	No	2AF233	Canada (commercial)	
		2AF283	Canada (commercial)	
		2AF234	US (investigational)	
		2AF284	US (investigational)	
Freezor® MAX Cardiac Cryoablation Catheter	No	209F3	Canada (commercial)	
		209F5	Canada (commercial)	
		239F3	US (investigational)	
		239F5	US (investigational)	

6.2. ArcticLine Cryoablation Catheter

The ArcticLine Catheter is a sterile, single use, minimally invasive intravascular catheter specifically designed for cardiac tissue cryoablation via a linear ablation segment. The ArcticLine Catheter is used together with the CryoConsole and related devices. The Catheter is percutaneously advanced to the applicable heart chamber from the femoral access via a transseptal sheath in the vasculature. The effective length is 107±2.0 cm. Once the catheter reaches the applicable atrium, it is positioned and the ablation segment creates a linear lesion at the targeted location. The ArcticLine Catheter is not approved for sale in any geography.

The proposed indication for the ArcticLine Catheter evaluated in this Study is as follows:

The ArcticLine Cardiac Cryoablation Catheter is indicated for creating endocardial linear lesions, subsequent to successful pulmonary vein isolation, during cardiac ablation procedures for treatment of patients with persistent atrial fibrillation. The ArcticLine Catheter can also be used to treat typical atrial flutter.

Note: Patients enrolled in the study must have persistent atrial fibrillation. For those subjects who also have concomitant typical atrial flutter or the investigator determines a prophylactic CTI line is warranted, the ArcticLine Catheter will be used to create a CTI line for treatment. Patients with stand-alone typical atrial flutter will not be enrolled in the study.

6.3. CryoConsole, including Accessories and Catheter File

The CryoConsole houses the electronics and software for controlling and recording the ablation procedure, stores and controls delivery of liquid refrigerant under high pressure through the co-axial umbilical to the catheter, recovers the expanded refrigerant vapor from the catheter under vacuum, and disposes of the refrigerant through the hospital scavenging system. The hardware controls the safety monitoring systems while the software provides the user interface subject information, procedure temperature, time set point in automatic mode and procedure data information.

The sterile coaxial umbilical delivers the Nitrous Oxide (N_2O) gas from the console to the catheter and transports refrigerant vapors from the catheter to the console, which is then vented into the hospital scavenging system.

The sterile electrical umbilical is an electrical extension cable that transports:

- Temperature feedback from the catheter to the console
- Leak detection signals from the catheter to the console
- Blood sensor signals from the catheter to the console
- Pressure sensor form the catheter to the console

The catheter file for each respective cryoablation device resides on the CryoConsole. When a catheter is connected to the console, the console searches for the catheter file associated with the connected catheter. The catheter file is read and the parameters from the file are used to configure the system accordingly.

The Arctic Front Advance and Freezor MAX catheter files are readily available on the CryoConsole at sites as they are market-released devices. Prior to study start at each site, the ArcticLine catheter file will be uploaded from a flash drive by Medtronic personnel to each CryoConsole expected to be used in the clinical study.

6.4. FlexCath Advance Steerable Sheath, 12 Fr

The FlexCath Advance Steerable Sheath, 12 Fr ("sheath") is a percutaneous introducer fitted with a hemostasis valve to allow for introduction, withdrawal and exchange of catheters and wires while providing a barrier preventing air ingress into the valve and minimizing blood loss. A side-port with stopcock is integrated into the hemostasis valve to allow continuous drip infusion, injection through the center lumen, flushing, aspiration, blood sampling and pressure monitoring. The sheath is intended to allow sheath deflection to facilitate catheter positioning. It is supplied sterile and packaged together with a dilator.

The Indications for Use in Canada and the US: The FlexCath Advance Steerable Sheath is intended for percutaneous catheter introduction into the vasculature and into the chambers of the heart. The sheath deflection facilitates catheter positioning.

Investigational Note: As the sheath Instructions For Use for both Canada and the US states it can accommodate devices up to 10.5Fr, and the ArcticLine Catheter is 11Fr, the sheath will be used investigationally for the purposes of the study.

6.5. Arctic Front Advance Cryoablation Catheter and Related Devices

The Arctic Front Advance ("AFA") Cardiac Cryoablation Catheter is a sterile, single use, minimally invasive intravascular balloon catheter specifically designed for tissue cryoablation. The AFA Catheter is used together with the CryoConsole and related devices. The AFA Catheter is percutaneously advanced to the heart chamber from the femoral access via a transseptal sheath in

the vasculature. Once the catheter reaches the left atrium, the balloon is inflated and the cooling segment creates circumferential lesions at the antrum of the targeted pulmonary veins.

Licensed indication in Canada: The Arctic Front Advance Cardiac Cryoablation Catheter is indicated for the treatment of patients with atrial fibrillation.

Approved indication in US: The Arctic Front Advance Cardiac Cryoablation Catheters are indicated for the treatment of drug refractory recurrent symptomatic paroxysmal atrial fibrillation.

Investigational Note: As the US Arctic Front Advance IFU does not include treatment of persistent atrial fibrillation, any use of the device at a US study center will be considered investigational.

The Achieve and Achieve Advance Mapping Catheter ("Achieve/Achieve Advance mapping catheter") and the Manual Retraction Kit are used in conjunction with the Arctic Front Advance catheter as described below.

The Achieve/Achieve Advance mapping catheter is an intra-cardiac electrophysiology diagnostic catheter indicated for multiple electrode electrophysiological mapping of the cardiac structures of the heart, i.e., recording or stimulation only. The Achieve/Achieve Advance mapping catheter is designed to obtain electrograms in the atrial regions of the heart.

The Indications for Use in Canada and the US: The Achieve/Achieve Advance mapping catheter is indicated for multiple electrode electrophysiological mapping of the cardiac structures of the heart, i.e. recording or stimulation only. The Achieve/Achieve Advance mapping catheter is designed to obtain electrograms in the atrial regions of the heart.

The Manual Retraction Kit contains one large syringe, one 3-way stopcock and a coaxial-to-Luer adaptor. The kit is used during the rewrap procedure of the Arctic Front Advance catheter if the Investigator cannot retract the catheter using the normal catheter retraction cycle.

6.6. Freezor MAX Cryoablation Catheter

The Freezor MAX Cardiac Cryoablation Catheter ("Freezor MAX") is a sterile, single use, flexible, steerable catheter used to ablate cardiac tissue. It is used together with the CryoConsole and related devices. The 8mm tip of the focal Freezor MAX reaches cryoablation temperatures when refrigerant is injected from the CryoConsole to the tip of the catheter. The catheter tip has an integrated thermocouple for temperature reading capability. The catheter is introduced into the vasculature by traditional minimally invasive techniques.

Licensed indication in Canada: The Freezor *MAX* Cardiac Cryoablation Catheter is intended for use in treatment of cardiac arrhythmias.

Approved indication in US: The Freezor MAX Cardiac Cryoablation Catheters is indicated for use as an adjunctive device in the endocardial treatment of paroxysmal atrial fibrillation in conjunction with the Arctic Front Advance Cardiac Cryoablation Catheter for the following uses: gap cryoablation to complete electrical isolation of the pulmonary veins, cryoablation of focal trigger sites and creation of ablation line between the inferior vena cava and the tricuspid valve.

Investigational Note: As the US Freezor MAX *IFU does not include treatment of persistent atrial fibrillation, any use of the device at a US study center will be considered investigational.*

6.7. Packaging

In Canada and the US, the ArcticLine Catheter will be labeled as investigational. The sheath will not be labeled as investigational, as this device will be considered investigational upon opening and introduction into the vasculature per the CIP. The Achieve/Achieve Advance mapping catheter will not be labeled as investigational, as these devices will be used on label in the Study.

In Canada, the AFA and Freezor MAX catheters will not be labeled as investigational, as these devices will be used on label in the Study.

In the US, the AFA and Freezor MAX catheters will not be labeled as investigational, as these devices will be considered investigational upon opening and introduction into the vasculature per the CIP.

6.8. Product Training Requirements

Investigators responsible as primary operators for the ablation procedure will be required to undergo product training prior to the site's first subject treatment. A separate training document will overview topics and include details on the format and frequency of delivery.

6.9. Product Receipt, Tracking and Return

The study will utilize the commercially available sheath, AFA and Freezor MAX with no study driven changes to the product or labeling. These devices will not be provided to the centers. Product tracking considerations by device type:

- Sheath: Considered investigational in both Canada and the US when opened and introduced into the vasculature.
- AFA: Considered investigational in the US when opened and introduced into the vasculature; non-investigational in Canada.
- Freezor MAX: Considered investigational in the US when opened and introduced into the vasculature; non-investigational in Canada.

The ArcticLine Catheter Files will be stored on flash drives and uploaded by Medtronic personnel (e.g. Field Clinical Engineers) to the CryoConsoles identified at each study site. The flash drives will not be handled directly by study site personnel and will remain in the possession of Medtronic personnel for the duration of study enrollment. Once a Catheter File is installed on a site's CryoConsole, Medtronic personnel will affix a label denoting the presence of investigational software. See Appendix A for the example text of the CryoConsole investigational label. Once study enrollment is completed, the ArcticLine Catheter File will be uninstalled from the CryoConsole by Medtronic personnel. Medtronic will manage the device accountability for the Catheter File and provide each site with a copy of the device disposition log.

The following products are to be returned to Medtronic by each study site:

- All ArcticLine Catheters, including expired catheters or those remaining after conclusion of the study
- Any AFA or Freezor MAX catheter with a reportable device deficiency
- Any sheath used in conjunction with an ArcticLine Catheter with a reportable device deficiency

Device disposition logs will be provided to all centers and used for tracking of all investigational product throughout the duration of the study, except for the Catheter File device disposition log which will be owned by Medtronic as noted above. The logs must be maintained and updated when product is disposed of or returned to Medtronic.

6.10. Product Storage

ArcticLine Catheters are investigational and will be maintained in locked, secure storage with access limited only to approved study staff.

7. Selection of Subjects

7.1. Study Population

The study population being studied are patients with documented persistent atrial fibrillation, or those with persistent atrial fibrillation and a history of, or inducible, typical atrial flutter, and generally good cardiovascular health.

7.2. Subject Enrollment

Patients will be screened to ensure they meet all inclusion criteria and none of the exclusion criteria prior to study enrollment, as appropriate. IRB/REB/MEC and Medtronic approval of this CIP and the patient Informed Consent Form must be obtained prior to enrolling subjects in the study. Enrollment of the subject must occur prior to performing any study procedures. Subjects are enrolled at the time the patient Informed Consent Form is signed and dated.

7.3. Inclusion Criteria

- Symptomatic persistent AF, defined as continuous AF that is sustained beyond 7 days and documented via consecutive ECG recordings
- Age 18 through 80 years old
- Failure or intolerance of at least one Class I or III antiarrhythmic drug
- Subject is able and willing to consent to participate in the study and will commit to completion of all follow-up requirements

7.4. Exclusion Criteria

- Longstanding persistent AF, defined as continuous AF greater than 12 month duration
- Left atrial diameter greater than 5.0 cm
- Active systemic infection
- History of thromboembolic event within the past 6 months or evidence of intracardiac thrombus at the time of the procedure
- Prior left atrial ablation attempt, with exception of:
    - Any pulmonary vein isolation attempt to treat AF, or
    - Successful ablation to treat Wolff-Parkinson White syndrome
- History of left atrial tachycardia
- History of cardiac ablation within 90 days of planned clinical study procedure

- Planned concomitant ventricular ablation[16]
- Cryoglobulinemia
- Structural heart disease of clinical significance including:
  - NYHA Class IV Heart Failure
  - Diagnosed with NYHA Class III Heart Failure for more than six months at time of the study ablation procedure
  - LVEF less than 35%
  - Any cardiac surgery (e.g. CABG) within 3 months of the ablation procedure
  - Any mechanical heart valve, prior aortic or tricuspid valve replacement (e.g. valvotomy, valve replacement), or tricuspid valve repair
  - Severe mitral valve regurgitation or stenosis
  - Significant congenital anomaly or anatomy unable to accommodate device
- Prior surgical maze procedure
- Unstable angina
- Myocardial infarction within 3 months of the ablation procedure
- Presence of primum or secundum atrial septal defect
- Anomalous pulmonary venous return
- Prior surgery for congenital heart disease, including atrial septal defect
- Hypertrophic cardiomyopathy with LV septal wall thickness >1.5 cm
- Uncontrolled hyperthyroidism
- Thrombocytosis, thrombocytopenia (including history of heparin-induced thrombocytopenia)
- Severe comorbidity or poor general physical/mental health that, in the opinion of the investigator, will not allow the subject to be a good study candidate
- History of blood clotting or bleeding abnormalities
- Contraindication to all anticoagulation (e.g. novel oral anticoagulants, heparin or warfarin)
- Pregnant, nursing or planning to become pregnant during study duration
- Enrollment in another clinical trial without prior approval from Medtronic
- Presence or use of left atrial appendage closure device
- Presence of or planned implantation of a pacemaker, implantable cardiac defibrillator, implantable loop recorder or cardiac resynchronization device with permanent lead placement
- Pre-existing hemidiaphragmatic paralysis
- Life expectancy less than one year
- Known drug or alcohol dependency

[16] Concomitant ventricular ablation will be allowed in the proposed feasibility clinical study if determined to be in the best interest of the subject at the time of the procedure as assessed by the Investigator. However, the ArcticLine Catheter may not be used for these purposes.

- Existing pulmonary vein stent(s)

Note: For exclusion criteria that cannot be fully assessed in a subject at the time of baseline, but are found to be met during the procedure (e.g. left atrial tachycardia, anatomy unable to accommodate the device), the subject will be exited from the study at that time.

8. Study Procedures

8.1. Schedule of Events

Data collection requirements are summarized in Table 3, below.

Table 3: Study Procedures and Data Collection by Subject Visit

	Baseline	Procedure	Pre-Discharge	1 week[1]	3 month[2]	6 month[2]	12 month[2]	Unscheduled	Repeat Ablation after Blanking
Informed Consent	X								
Inclusion/Exclusion Criteria	X								
Medical History	X								
Physical Exam	X								
AAD & Anticoagulation Medication Review	X		X	X	X	X	X	X	
Pregnancy Screen[3]	X								
Arrhythmia Symptom Review	X			X	X	X	X	X	
Transthoracic Echocardiogram (TTE)[4]	X								
Transesophageal Echocardiogram (TEE)	X								
12 Lead ECG	X		X		X	X	X	X	
Procedure Information		X							X
24 Hr Continuous Monitoring with Holter						X	X		
Patient Activated Ambulatory ECG Monitor					Monthly and symptomatic episodes				
Adverse Events	As they occur								
Device Deficiencies	As they occur								
Study Deviations	As they occur								

Notes:

[1]Phone visit and/or office visit with Nurse Coordinator

[2]Office visit

[3]Female subjects of child bearing potential only

[4] Only required if data not available from within 6 months prior to consent date

8.2. Subject Consent

Patient informed consent (IC) is defined as a legally effective documented confirmation of a subject's (or their legally authorized representative) voluntary agreement to participate in a particular clinical study after information has been given to the subject on all aspects of the clinical study that are relevant to the subject's decision to participate. This process includes obtaining a IC Form and an Authorization to Use and Disclose Personal Health Information (US only) that has been approved by the study center's IRB/REB/MEC and signed and dated by the subject or their legally authorized representative. A subject may only consent 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. Informed consent may be given by their legally authorized representative only if a subject is unable to make the decision to participate in a clinical investigation. In such cases, the subject shall also be informed about the clinical investigation within his/her ability to understand.

Prior to enrolling subjects, the IC Form must have been approved by each center's IRB/REB/MEC. Each site must also use an Authorization to Use and Disclose Personal Health Information/Research Authorization (US only) or other privacy language as required by law. The IC Form must be controlled (i.e. versioned and/or dated) to ensure it is clear which version(s) were approved by the IRB/REB/MEC. Any adaptation of the sample IC Form must be reviewed and approved by Medtronic and the IRB/REB/MEC reviewing the application prior to enrolling subjects.

The Investigator must notify the subject (or their legally-authorized representative) of any significant new findings about the study that become available during the study which are pertinent to the safety and well-being of the subject. This could impact a subject's willingness to participate in the study. If relevant, approval may be requested from subjects to confirm their continued participation.

Prior to initiation of any study-specific procedures, documented informed consent must be obtained from the subject (or their legally authorized representative). Likewise, privacy or health information protection regulation may require subjects to sign additional forms to authorize centers to submit subject information to the study sponsor. The informed consent process must be conducted by the Principal Investigator or an authorized designee, and the IC Form and the Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language (US only) as required by law must be given to the subject (or their legally authorized representative) in a language he/she is able to read and understand. The process of informed consent must be conducted without using coercion, undue or improper influence on, or inducement of the subject to participate by the Investigator or other center personnel. The informed consent process shall not waive or appear to waive the subject's legal rights. The language used shall be as non-technical as possible and must be understandable to the subject and the impartial witness, where applicable.

The subject must have ample time and opportunity to read and understand the IC Form, to inquire about details of the study, and to decide whether to participate in the clinical study. All questions about the study should be answered to the satisfaction of the subject.

When the subject decides to participate in the clinical study, the IC Form and the Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language (US only) as required by law must be signed and personally dated by the subject (or their legally authorized representative) and either the Investigator or the Investigator's authorized designee, as required by local law. If applicable, witness shall also sign and personally date the consent form to attest that the information in the IC Form was accurately explained and clearly understood by the subject, and that informed consent was freely given.

A copy of the IC Form and the Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language as required by law (US only), signed and dated as required by law, must be provided to the subject.

If consent is obtained the same day the subject begins participating in study-related procedures, it must be documented in the subject's case history that consent was obtained prior to participation in any study related procedures. It is best practice for the informed consent process to be documented in the subject's case history, regardless of circumstance.

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

The original of the signed IC Form and the Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language (US only) as required by law must be filed in the hospital/clinical chart and/or with the subject's study documents and should also be available for monitoring and auditing. Any Medtronic Field personnel who support the study procedure must be able to review the subject's signed and dated IC Form and verify its completeness prior to proceeding with the procedure. In the event the Medtronic Field personnel identify an IC Form as being incomplete, the study procedure will not be allowed to occur until the consent of the subject can be adequately and appropriately obtained.

8.3. Baseline and Pre-Ablation Procedure

The baseline visit can be a standalone visit or can be performed on the same day but prior to the cryoablation procedure. The following evaluations will be performed after consent, unless previously performed as part of routine clinical evaluations within the specified windows:

Within 6 months prior to consent date:

- Transthoracic echocardiogram (TTE) for the collection of left atrial diameter, left ventricular ejection fraction, and mitral valve impairment. A repeat TTE procedure for the Study after the consent date is not required if a TTE was performed within 6 months of the consent data and all data are available.

After consent date but prior to procedure:

Note: The time between the consent date and the procedure should not exceed 30 days. If 30 days are exceeded, the subject must be re-evaluated against inclusion and exclusion criteria to ensure they still qualify for the study.

- Assessment of all factors specified for evaluation under Inclusion Criteria and Exclusion Criteria (see Sections 7.3 and 7.4, respectively).
    - Note: After required study testing, if a subject no longer meets the inclusion criteria or now meets exclusion criteria, the subject will be exited from the study.
- Demographics
- Medical history
- Physical examination
- Pregnancy screen (female subjects of child bearing potential only)
- 12 lead ECG
- Record rhythm and class I and III AAD and anticoagulation medications
- Transesophageal Echocardiogram (TEE):
    - TEE will be performed in all subjects within 2 days prior to, including day of, planned ablation procedure.
    - Subject will not proceed with the study ablation procedure and will be exited from the study if presence of atrial thrombus is identified.

8.4. Procedure

The Investigator is to perform the procedure according to the procedural steps in this CIP and the applicable Instructions for Use for all devices (except for investigational uses as described in this CIP). Current recommendations for anticoagulation are found in the 2017 HRS/EHRA/ECAS/APHRS/SOLAECE Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation[2] and 2014 Focused Update on the Canadian Cardiovascular Society Guidelines for the Management of Atrial Fibrillation.[17]

8.4.1. High Level Procedure Overview:

Appropriate sedation and venous access should be attained per the Investigator's standard practice according to their institution's pre-established procedures/guidelines at the time of the procedure. Investigator may choose compatible guidewires and mapping catheters at their discretion. The FlexCath Advance 12Fr sheath must be used. Deploy diagnostic catheters and perform transseptal puncture.

Perform a baseline voltage map of the left atrium using a 3D mapping system (e.g. NavX, Rhythmia). Recommended settings for minimum voltage in this study is 0.2mV.

Perform baseline mapping of the pulmonary veins to assess for pulmonary vein potentials using a circular mapping catheter (e.g. Achieve Advance) to determine if PVI is required. If yes, perform the pulmonary vein isolation procedure using Arctic Front Advance Catheter as per Section 8.4.5.

If PVI ablation is performed, repeat voltage mapping of the left atrium using a 3D mapping system.

If the investigator determines the subject should move forward with ArcticLine ablation, perform the following required linear ablations using the ArcticLine Catheter as per Section 8.4.6:

- Left atrial roof line
- Left atrial posterior wall line

Note: An example where the investigator may choose not to move forward with ArcticLine ablation and instead, exit the subject from the study, is when a subject has previously undergone PVI and has minimal pulmonary vein reconnection which, in the opinion of the investigator, only requires touch-up ablation.

[17] Verma A, et al. 2014 Focused Update of the Canadian Cardiovascular Society Guidelines for the Management of Atrial Fibrillation. *Canadian Journal of Cardiology.* 30 (2014) 1114-1130.

At the investigator's discretion, perform optional linear ablations at the following anatomic targets using the ArcticLine Catheter:

- Mitral isthmus (see Section 8.4.7)
- CTI (see Section 8.4.8)

At the investigator's discretion, use pacing maneuvers to determine the immediate effect of the ArcticLine ablation(s). Note: Direct Current (DCCV) or pharmacological cardioversion may be considered at any point during the procedure when restoration of SR will assist in assessing the effectiveness of cryoablations or deemed necessary for the benefit of the patient.

Repeat ArcticLine ablation(s), as necessary to achieve conduction block, as described in Sections 8.4.6-8.4.8 .

Upon completion of a minimum 30-minute wait time from the last ArcticLine ablation for each respective anatomy target, perform repeat voltage map of the left atrium using a 3D mapping system with the recommended settings. Use of 3-D mapping following the 30-minute waiting period should be performed while the subject is in Sinus Rhythm.

Notes:

- Reference ArcticLine Technical Guidance for recommendations on pacing maneuvers and 3D mapping settings.
- If Investigator is unable to successfully complete a lesion with the ArcticLine Catheter after a minimum of four (4) ArcticLine ablation applications, they may cross over to another FDA approved catheter. This will be considered an ArcticLine treatment failure.
- Temperatures of –80ºC are expected with use of the ArcticLine Catheter.
- Methods used to assess for conduction block must be documented and reported.
- Copies of voltage maps from ArcticLine procedures are to be sent to Medtronic.

8.4.2. Esophageal Visualization and Temperature Monitoring

Ensure an esophageal temperature monitor is used for each cryoablation application (Arctic Front Advance if applicable and ArcticLine). Cease cryoablation if the temperature reaches ≤25°C[2]. Use of proton pump inhibitors (PPI) is recommended in all ArcticLine Catheter-treated subjects for at least 6 weeks post-procedure or longer as per institutional standard of care to reduce the risk of esophageal injury.

8.4.3. Peri-Procedural Anticoagulation

Heparin should be administered prior to or immediately following transseptal puncture during AF ablation procedures and adjusted to achieve and maintain an ACT of 300 to 400 seconds, or per standard center guidelines, and checked approximately every 30 minutes. Performance of AF ablation in a subject systemically anticoagulated with warfarin or novel oral anticoagulants (NOACs) does not alter the need for intravenous heparin to maintain a therapeutic ACT during the procedure. Administration of protamine following ablation to reverse heparin should be considered.

8.4.4. Diaphragm Movement

Continuous pacing of the applicable phrenic nerve must be performed for each anatomic target as noted in Table 4. Additional methods of phrenic nerve monitoring are recommended.

Table 4: Required Phrenic Nerve Pacing

Anatomic Target	Right Phrenic Nerve Pacing	Left Phrenic Nerve Pacing
Right-sided pulmonary veins (if applicable)	Required	Not applicable (N/A)
Left-sided pulmonary veins (if applicable)	Optional	Optional
Roof	Required	N/A
Posterior wall	Required	N/A
Mitral isthmus (if applicable)	N/A	Required
Cavotricuspid isthmus (if applicable)	Required	N/A

8.4.5. Pulmonary Vein Cryoablation with Arctic Front Advance Catheter

Subjects will be evaluated to determine the need for PVI. If the need is confirmed based on intracardiac electrogram recordings, every effort consistent with subject welfare should be made to treat all PVs or their anomalous equivalents where electrical activity is noted.

Subjects in the Study who require pulmonary vein isolation are to be treated as follows:

- As stated in Section 8.4, perform a baseline voltage map of the left atrium using a 3D mapping system.
- Ablate the pulmonary veins using the Arctic Front Advance Catheter according to the IFU.
- Each pulmonary vein must be assessed for entrance block to demonstrate electrical isolation. Optionally, pulmonary vein assessment for exit block may be performed.
- Perform repeat voltage mapping of the left atrium using a 3D mapping system.

Notes:

- Upon the Investigator's assessment of procedure completion, Isoproterenol and/or adenosine may be used to further assess pulmonary vein isolation.
- Freezor MAX should be used for any gap completion or other FDA approved ablation catheter. In the event Freezor MAX is not used for gap completion, the subject will be exited from the study.

8.4.6. Linear Cryoablation with ArcticLine Catheter: Roof and Posterior Wall

Once confirmation all pulmonary veins have been isolated and the investigator determines the subject should move forward with ArcticLine ablation, perform the following steps:

Withdraw and remove the Arctic Front Advance catheter through the FlexCath Advance sheath.

Insert and advance ArcticLine Catheter into the left atrium via the FlexCath Advance sheath and position as follows:

- Roof: Position the ArcticLine Catheter between the right and left superior pulmonary veins.
- Posterior wall: Position ArcticLine Catheter between the inferior pulmonary veins.

Repeat the following steps for both the roof and posterior wall locations:

- Assess the positioning and contact via fluoroscopy, ultrasound imaging, or other visualization technique. Reposition as needed.
- Perform the cryoablation. Cryoapplications of three (3) minutes is recommended for the roof and posterior wall targets in the left atrium.
- At the investigators discretion, use pacing maneuvers to determine the immediate effect of the ArcticLine ablation(s).
- Note: It is the investigator's discretion to assess necessity of additional freezes to complete the desired ablation line.

Once the roof line and posterior wall lines are completed, assess the posterior wall for isolation using pacing maneuvers and/or 3D mapping.

If no further ArcticLine ablation(s) in the left atrium will be performed:

- Repeat voltage mapping of the left atrium using a 3D mapping system after a minimum 30-minute wait time from the last ArcticLine ablation for each respective anatomy target.
- Use of 3-D mapping following the 30-minute waiting period should be performed while the subject is in Sinus Rhythm.

Notes:

- Upon the Investigator's assessment of procedure completion, Isoproterenol and/or adenosine may be used to further assess pulmonary vein conduction.
- Freezor MAX may be used at the investigators discretion to touch up gaps in conduction if complete pulmonary vein isolation was not achieved with the Arctic Front Advance.

8.4.7. Linear Cryoablation with ArcticLine Catheter: Mitral Isthmus

If the investigator chooses to perform a mitral isthmus line ablation, perform the following steps:

Advance the ArcticLine Catheter to the mitral isthmus by positioning between the mitral annulus and either posteriorly to the left inferior pulmonary vein or anteriorly to the left superior pulmonary vein.

Assess the positioning and contact via fluoroscopy, ultrasound imaging, or other visualization technique. Reposition as needed.

Perform the cryoablation. Cryoapplications of three (3) minutes is recommended at the mitral isthmus.

- Note: It is the investigator's discretion to assess necessity of additional freezes to complete the desired ablation line.

Assess for bi-directional conduction block across the mitral isthmus, while subject is in sinus rhythm, using pacing maneuvers and/or 3D mapping following ArcticLine ablation.

- Note: Direct Current (DCCV) or pharmacological cardioversion should be performed prior to assessing patient for conduction block.

If no further ArcticLine ablations in the left atrium will be performed:

- Reconfirm bi-directional conduction block at the mitral isthmus following a 30 minute wait from the last ArcticLine ablation.
- Repeat voltage mapping of the left atrium using a 3D mapping system after a minimum 30-minute wait time for each respective ArcticLine lesion.
- Use of 3-D mapping following the 30-minute waiting period should be performed while the subject is in Sinus Rhythm.
- Local Activation Time (LAT) Mapping to further confirm conduction block following a 30-minute wait may be considered.

Notes:

- Upon the Investigator's assessment of procedure completion, Isoproterenol and/or adenosine may be used.
- Freezor MAX should be used if gap completion is required.

8.4.8. Linear Cryoablation with ArcticLine Catheter: Cavotricuspid Isthmus

If the investigator chooses to perform a CTI line ablation, perform the following steps:

Advance the ArcticLine Catheter to the CTI by positioning between the inferior vena cava and tricuspid annulus.

Assess the positioning and contact via fluoroscopy, ultrasound imaging, or other technique. Reposition as needed.

Perform the cryoablation. Cryoapplications of four (4) minutes is recommended at the CTI.

- Note: It is the investigator's discretion to assess necessity of additional freezes to complete the desired ablation line.

Assess the CTI line for bi-directional conduction block using pacing maneuvers and/or 3D mapping following a 30-minute wait.

Notes:

- Upon the Investigator's assessment of procedure completion, Isoproterenol and/or adenosine may be used.
- Note: Freezor MAX should be used if gap completion is required.

8.4.9. Cardioversion

Direct Current (DCCV) or pharmacological cardioversion may be considered at any point during the procedure when restoration of SR will assist in assessing the effectiveness of cryoablations or deemed necessary for the benefit of the patient. Electrical or pharmacological cardioversion to sinus rhythm must be attempted at the conclusion of the procedure if sinus rhythm was not restored.

8.4.10. Role of Medtronic Personnel at Study Procedure

Medtronic personnel will collect procedural data from the CryoConsole post-procedure via data download. It is the responsibility of the study center to ensure the subject is identified via subject ID number when entered into the system to prevent the distribution of personally identifiable information.

8.5. Hospital Discharge

At or shortly before hospital discharge, the following will be performed and collected:

- Adverse event assessment
- Review medications
- 12 lead ECG
- Review study requirements with the subject to help ensure compliance with follow-up procedures

Systemic anticoagulation with warfarin or a direct thrombin or Factor Xa inhibitor is recommended for at least two months following the AF ablation procedure; however, the anticoagulation treatment will be at the Investigator's discretion according to established guidelines. Decisions regarding the continuation of systemic anticoagulation agents more than two months following ablation should be based on the subject's risk factors for stroke and not on the presence of AF.

Use of proton pump inhibitors (PPI) is recommended in all ArcticLine Catheter-treated subjects for at least 6 weeks post-procedure or longer as per institutional standard of care to reduce the risk of esophageal injury.

8.6. Medications

It is recommended to discontinue the use of Class I and III antiarrhythmic medication by the end of the 90 day post-procedure blanking period.

Information regarding medications prescribed for anticoagulation, proton pump inhibitors, or to treat atrial arrhythmias (including adenosine and isoproterenol use during the ablation procedure), will be collected from subject enrollment through study exit, including the medication name, dose and frequency.

8.6.1. Class I and III antiarrhythmic medication use after the 90 day post-procedure blanking period

- Subjects may re-initiate, at any point during follow-up, a Class I or III antiarrhythmic medication that failed or was not tolerated prior to the ablation procedure at the same or lower dose.
- Initiation of a new Class I or III antiarrhythmic medication or a dose increase after the blanking period will be considered a treatment failure.
- All medications are permitted in the study except for investigational drugs that may confound the study results.

8.7. Permissible Repeat Cryoablation

Repeat ablation, following the same procedure described in Section 8, is allowed one time within the 90 day post-procedure blanking period.

- Durability of all lesions, including pulmonary vein and linear lesions, will be assessed for gaps prior to re-ablating target locations.
- Ablation of linear lesions, outside of those described in Section 8, will be considered a treatment failure.
- Linear ablation using RF in the left or right atria will be considered a treatment failure with the exception of subjects who did not undergo CTI ablation with the ArcticLine Catheter in their index study procedure.
- Pulmonary vein ablation touch-up using RF will be considered a treatment failure.

Repeat ablation procedures will be documented on an electronic case report form (eCRF). The subject's procedures and follow-up windows will continue based on the index ArcticLine Catheter ablation procedure date.

8.8. Scheduled Follow-up Visits

After receiving notice of a completed study procedure, Medtronic will provide the target dates and windows for each visit to the center. Should a subject miss a visit or the visit fall outside the pre-specified window, a study deviation must be reported and the original follow-up schedule maintained for subsequent visits.

Data analyses include follow-up visits, regardless of whether the visit occurs within the window. Therefore, a late visit is preferred over a missed visit but must be accompanied by a deviation. Follow-up visit windows are listed in Table 5 and are based on days after the index ArcticLine Catheter ablation procedure.

Table 5: Follow-up Schedule

Occurrence/ Visit	Window (Calculated days after the ablation procedure)	
	Window Start	**Window End**
Enrollment/Baseline[1]	-30 days	Day 0
Index ArcticLine Procedure	Day 0	Day 0
1 week phone or office	7 days	14 days
3 month office	91 days	105 days
6 month office	165 days	179 days
12 month office	365 days	379 days
[1]*Note: If the time between the consent date and the procedure exceeds 30 days, the subject must be re-evaluated against inclusion and exclusion criteria to ensure they still qualify for the study.*		

The following information is required to be collected at the follow-up visits:

8.8.1. One Week Phone or Office Visit

- Review medications
- Adverse event assessment
- Review symptoms suggestive of recurrent AF/AT/AFL

8.8.2. Three Month Office Visit

- Review medications
- Adverse event assessment
- Review symptoms suggestive of recurrent AF/AT/AFL
- 12 lead ECG
- Provide the subject with patient activated ambulatory monitoring equipment and provide instructions for monthly and symptomatic transmissions

8.8.3. Six Month Office Visit

- Review medications
- Adverse event assessment
- Review symptoms suggestive of recurrent AF/AT/AFL
- 12 lead ECG
- 24-hour continuous monitoring with Holter
- Remind subject of instructions on patient activated ambulatory monitoring equipment for monthly and symptomatic transmissions

8.8.4. Twelve Month Office Visit

- Review medications
- Adverse event assessment
- Review symptoms suggestive of recurrent AF/AT/AFL
- 12 lead ECG
- 24-hour continuous monitoring with Holter
- Collect or ensure return of ambulatory monitoring equipment

8.8.5. Unscheduled Office Visits

An unscheduled visit is defined as any unplanned cardiovascular-related office visit or early study exit at the study center that occurs between CIP required visits. If the subject exits the study early, an unscheduled office visit should occur. The following information is required to be collected at unscheduled follow-up visits:

- Review medications
- Adverse event assessment
- Review symptoms suggestive of recurrent AF/AT/AFL
- 12 lead ECG

8.8.6. Holter and Patient Activated Ambulatory ECG Monitoring

Market-released Holters will be distributed by a core lab to centers after activation has occurred. All subjects will wear a Holter in conjunction with their 6 and 12 month office visits. Holters will be sent to the core lab after they have been worn by the subject. The core lab will be responsible for adjudication of atrial arrhythmias. The core lab will manage maintenance, calibration and tracking of the Holters.

Market-released Patient Activated Ambulatory ECG Monitors will be distributed by a core lab to centers after activation has occurred. All subjects will transmit monthly and symptomatic ECGs following their 3 month office visit. The monitors will be returned to the core lab at the end of the study. The core lab will be responsible for adjudication of atrial arrhythmias. The core lab will manage maintenance, calibration and tracking of the monitors.

8.8.7. 12 Lead Electrocardiograms

All 12 lead ECGs will be sent to the core lab. The core lab will be responsible for adjudication of atrial arrhythmias. Copies of additional source documents may be requested.

8.9. Assessment of Safety

The primary safety objective is based on the Adverse Event data collected. Further information on the collection of Adverse Events is discussed in Section 10.

8.10. Recording Data

The study will collect data using an electronic data management system for clinical studies. Centers will enter data onto case report forms (CRFs) within the electronic database. The Holter/Patient Ambulatory Monitoring/12-lead ECG core lab will also provide data in the electronic database.

Data reported on the CRFs shall be derived from source documents, which may include worksheets, patient medical records and ECG data. These source documents must be maintained by the center personnel. Further detail on data management is provided in Section 14.2.

8.11. Deviation Handling

A study deviation is defined as an event within a study that did not occur according to the CIP or the Clinical Trial Agreement. Prior approval by Medtronic is expected in situations where the Investigator anticipates, contemplates, or makes a conscious decision to deviate. If the deviation affects subject's rights, safety and well-being, or the scientific integrity of the study, prior approval from IRB/REB/MEC may also be required, depending on local requirement. Prior approval is not required when a deviation is necessary to protect the safety, rights or 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). Subjects' failure to submit ambulatory monitoring transmissions per the CIP does not require a deviation to be reported. Ambulatory monitoring transmission compliance will be tracked by Medtronic personnel and the Core Lab.

For medically justifiable conditions which preempt a subject's ability to complete a study-required procedure, it may be permitted to report only one deviation 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 endpoint analysis). However, prior approval from Medtronic is required for such situations.

All study deviations must be reported on the eCRF regardless of whether medically justifiable, pre-approved by Medtronic, an inadvertent occurrence, or taken to protect the subject in an emergency. The deviation description must be recorded with an explanation for the deviation.

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 IRB/REB/MEC as well as Medtronic within five (5) working days. Reporting of all other study deviations should comply with IRB/REB/MEC 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.

Medtronic is responsible for analyzing deviations, assessing their significance, and identifying any additional corrective and/or preventive actions (e.g. CIP amendment, conduct additional training, terminate the investigation). Repetitive or serious Investigator compliance issues may result in initiation of a corrective action plan with the Investigator and center, and in some cases, necessitate suspending enrollment until the problem is resolved 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 center on a periodic basis.

8.12. Subject Withdrawal or Discontinuation

A subject can withdraw from the study at any time. If the subject wishes to exit early from the study, the center is required to document the reason for exit on an eCRF and in the subject's medical record. In addition, centers shall follow the regulations set forth by their IRB/REB/MEC.

It is recommended that Investigators follow the subject until all device and/or procedure-related adverse events are recovered / resolved or unresolved with no further actions planned. Following completion of the 12 month visit or early study exit, subjects will continue to receive standard medical care. All data available through the time of the subject's exit will be used for analysis.

Reasons for early study exit include:

- Subject lost to follow-up
- Subject did not meet inclusion/exclusion criteria after consent and did not undergo an ablation procedure
- ArcticLine Catheter was not used during the subject's ablation procedure
- Subject did not provide consent or data use protection authorization
- 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.

In the case that the subject is determined to be lost to follow-up, details of a minimum of two attempts and the method of attempt (e.g., one letter and one phone record or two letters) to contact the subject must be recorded.

An unscheduled office visit should be attempted if the subject exits the study outside of a scheduled follow-up visit. Subjects treated with the ArcticLine Catheter who exit from the study should continue to be followed by an electrophysiologist for follow-up of any potential adverse events at the recommended interval of 12 months from the index ArcticLine Catheter ablation procedure.

For subjects who have not undergone treatment with the ArcticLine Catheter, a new subject may be enrolled to achieve the target sample size of N=30 treated subjects in the Study.

9. Risks and Benefits

9.1. Potential Risks

Medtronic follows rigorous Quality Assurance and Control procedures throughout the life of a product, from the business analysis phase through development, market release, and post-market surveillance. The ArcticLine Catheter has been examined and tested via modeling, bench, and pre-clinical animal testing and the residual risks associated with the ArcticLine Catheter have been found to be acceptable. These residual risks have been mitigated to the fullest extent possible through design, manufacturing, labeling and training. The potential benefits related to the use of the ArcticLine Catheter have been determined to outweigh any potential risks.

There are potential risks and side effects associated with ablation procedures. The Investigator shall describe risks in further detail when asked by the subject. The ArcticLine Catheter has not been approved for use in any geography. Therefore, the risks must be continuously monitored, assessed and documented by the Investigator. Possible additional risks for participating in the study include the following (although others are possible) and are further defined in Appendix C:

- Access site complications (e.g. bruising, ecchymosis)
- Anemia
- Anxiety
- Arrhythmia (e.g. atrial flutter, bradycardia, heart block, tachycardia)
- Back pain
- Bleeding, possibly requiring transfusion
- Bronchitis
- Cardiac tamponade
- Cardiopulmonary arrest
- Catheter entrapment in cardiac structures requiring intervention
- Cerebral vascular accident
- Chest discomfort/pain/pressure
- Cold feeling
- Coronary artery spasm
- Cough
- Death
- Diarrhea
- Dizziness
- Embolism
- Esophageal damage (including atrioesophageal fistula)
- Fatigue
- Fever
- Headache
- Hemoptysis
- Hypotension/hypertension
- Infection (e.g. sepsis)
- Lightheadedness
- Myocardial infarction
- Nausea/vomiting
- Perforation
- Pericardial effusion
- Pericarditis
- Phrenic nerve injury
- Pleural effusion
- Pneumonia
- Pneumothorax
- Pulmonary vein stenosis

- Pseudoaneurysm
- Pulmonary edema
- Pulmonary vein stenosis
- Shivering
- Shortness of breath
- Sore throat
- Transient ischemic attack
- Urinary tract infection
- Vagal nerve injury (e.g. gastroparesis)
- Valve damage with potential regurgitation
- Vasovagal reaction
- Visual change

9.2. Potential Benefits

The ArcticLine Catheter, designed to create linear cardiac lesions which interrupt errant electrical signals, may reduce or eliminate persistent atrial fibrillation in subjects with confirmed pulmonary vein isolation; however, some subjects may not receive this benefit. Using ArcticLine to create linear lesions may result in shorter procedure times, and contain fewer gaps, than lines created with traditional point-by-point technology resulting in the possibility of less fluoroscopy and anesthesia exposure to subjects. Additionally, the ArcticLine Catheter may be an improved technology over RF ablation in creating lesions that are not only continuous but transmural and durable.

Clinical benefit has not been demonstrated as this study is the first human use of the ArcticLine Catheter. The information gained from the study could result in improved management of atrial fibrillation.

9.3. Risk-Benefit Rationale

The cohort of subjects for inclusion in the study is symptomatic as a result of their persistent atrial fibrillation and the failure of Class I or III antiarrhythmic drug therapy. Alternatives to creation of linear lesions with the ArcticLine Catheter in this cohort includes pulmonary vein isolation alone or point-by-point linear ablation using RF technology. Investigation into the former with AFA is currently ongoing; the latter has not proven efficacy in this population, possibly due to the lack of durable transmural lesions[15] and/or understanding of the underlying substrate[18].

Cryoablation therapy offers the opportunity to reduce the episodes of atrial fibrillation and therefore reduce the subject's risk of stroke and symptoms. The use of the ArcticLine Catheter, a technology that can create a linear lesion with fewer applications, may reduce the potential for gaps through creation of a contiguous line. This may prevent recurrence of atrial fibrillation and typical atrial flutter as well as onset of new atrial tachycardia/atrial flutter.

[18] Zakeri, et al. The burden of proof: The current state of atrial fibrillation prevention and treatment trials. Heart Rhythm. 2017;14:763-782.

Increases in possible risks from the use of the ArcticLine Catheter when used in conjunction with the Arctic Front Advance Catheter include longer procedure times, more exposure to radiation through increased use of fluoroscopy, and increased left atrial dwell time.

Results of this feasibility study are expected to be used to guide subsequent product development activities for the ArcticLine Catheter, including an eventual pivotal study; the goal of which is to confirm meaningful therapeutic benefit of the ArcticLine Catheter to create linear lesions. After careful review of the risks and benefits, the benefits are found to outweigh the risks and justify this investigation of the ArcticLine Catheter in this underserved population.

10. Adverse Events and Device Deficiencies

10.1. Definitions/Classifications

Timely, accurate, and complete reporting and analysis of safety information for clinical studies are crucial for the protection of subjects. 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. The study is conducted in accordance with these procedures and regulations.

Since the safety reporting requirements and classification systems vary for each regulatory agency, requirements from all participating geographies are taken into account for the collection and reporting of safety information.

10.2. Adverse Event and Device Deficiency Definitions

Table 6: Adverse Event and Device Deficiency Definitions

General	
Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device NOTE 1: This definition includes events related to the investigational medical device or the comparator. NOTE 2: This definition includes events related to the procedures involved. NOTE 3: For users or other persons, this definition is restricted to events related to investigational medical devices. (ISO 14155:2011, 3.2)
Adverse Device Effect (ADE)	Adverse event related to the use of an investigational medical device NOTE 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. NOTE 2: This definition includes any event resulting from an error use or from intentional misuse of the investigational medical device. (ISO 14155:2011, 3.1)

Device Deficiency (DD)	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. NOTE: Device deficiencies include malfunctions, use errors and inadequate labeling (ISO 14155:2011, 3.15)
Relatedness	
Procedure related	An Adverse Event directly related to any portion of the procedure.
System related	An Adverse Event that results from the presence or performance (intended or otherwise) of the system (including the ArcticLine Catheter, CryoConsole, Arctic Front Advance, Freezor MAX, FlexCath Advance Sheath, Achieve Mapping Catheter, Manual Retraction Kit)
Cardiovascular related	An Adverse Event relating to the heart and the blood vessels or the circulation.
Not Related	Relationship to the device or procedures can be excluded when: • The event is not a known side effect of the product category the device belongs to or of similar devices and procedures; • The event has no temporal relationship with the use of the device or the procedures; • The serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; • The discontinuation of medical device application or the reduction of the level of activation/exposure – when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure) do not impact the serious event; • The event involves a body-site or an organ not expected to be affected by the device or procedure; • The serious event can be attributed to another cause (e.g., an underlying or concurrent illness/clinical condition, an effect of another device, drug, treatment, or other risk factors);

	• The event does not depend on a false result given by the device used for diagnosis (when applicable); • Harms to the subject are not clearly due to use error; • In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the event.
Unlikely	The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
Possible	The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.
Probable	The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained.
Causal Relationship	The event is associated with the device or study procedures beyond reasonable doubt when: ▪ The event is a known side effect of the product category the device belongs to or of similar devices and procedures; ▪ The event has a temporal relationship with device use/application or procedures; ▪ The event involves a body-site or organ that the device or procedures are applied to or the device or procedures have an effect on; ▪ The serious event follows a known response pattern to the medical device (if the response pattern is previously known); ▪ The discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its

	use (or increase of the level of activation/exposure) impact on the serious event (when clinically feasible); ▪ Other possible causes (e.g., an underlying or concurrent illness/clinical condition or/and an effect of another device, drug, or treatment) have been adequately ruled out; ▪ Harm to the subject is due to error in use; ▪ The event depends on a false result given by the device used for diagnosis (when applicable); ▪ In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.
Seriousness	
Serious Adverse Event (SAE)	Adverse event that a) led to death, b) led to serious deterioration in the health of the subject, that either resulted in: 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, or 3) in-patient or prolonged hospitalization (>24 hours), or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, c) led to fetal distress, fetal death or a congenital abnormality or birth defect NOTE 1: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event. (ISO 14155:2011, 3.37)
Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. (ISO 14155:2011, 3.36)

Unanticipated Adverse Device Effect (UADE)	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, an (investigational) device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the CIP or applicable (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. (21 CFR 812.3(s))
Unanticipated Serious Adverse Device Effect (USADE)	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report. NOTE: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report. (ISO 14155:2011 3.42)
Other	
Unavoidable Adverse Event	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 those provided below. These are not reportable AEs unless they occur after or last longer than the timeframe specified. If any other events below are classified as serious they must be reported as an adverse event.

Event Description	Timeframe (hours) from the Surgical Procedure
Anesthesia related nausea / vomiting	24
Low-grade fever (<100°F or 37.8°C)	48
Mild to moderate bruising / ecchymosis in groin area / groin pain	168
Sleep problems (insomnia)	72
Back pain related to laying on table	72

10.3. Reporting of Adverse Events, including Death

For the purposes of the study, all Adverse Events will be collected starting at the time of signing the IC Form through the duration of the subject's participation in the study.

Reporting of these events to Medtronic will occur on an AE eCRF, including a description of AE, date of onset of AE, date of awareness of center, treatment, resolution, assessment of both the seriousness and the relatedness to the investigational device. Each AE must be recorded on a separate AE eCRF. Exceptions include:

- Documented pre-existing conditions are not considered AEs unless the nature or severity of the condition has worsened. Additionally, arrhythmia episodes that are not new or worsening conditions and for which no action is taken are not reportable as AEs.
- Unavoidable Adverse Events, listed in Table 6: Adverse Event and Device Deficiency Definitions need not be reported unless the adverse event worsens or is present outside the stated timeframe after the ablation procedure.
- Cardioversions (DC or Drug) for recurrent symptomatic atrial fibrillation and other atrial arrhythmias are not considered serious adverse events

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

For any changes in status of a previously reported adverse event (i.e. change in actions taken, change in outcome, change in relatedness), an update to the original AE must be provided. All adverse events must be followed until the adverse event has been resolved, the subject exits the study or until study closure, whichever occurs first.

At the time of study exit, all collected AEs with an outcome of "not recovered/not resolved", "recovering/resolving" or "unknown" must be reviewed and updates provided as applicable.

All reported adverse events will be reviewed by a Medtronic representative. AEs will be classified according to the definitions provided.

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 that could have led to a SADE will be completed according to local regulatory requirements. Refer to Table 7 for a list of required Investigator and Medtronic reporting requirements and timeframes. It is the responsibility of the Investigator to abide by any additional AE reporting requirements stipulated by the IRB/MEC responsible for oversight of the study.

For a list of Foreseeable Adverse Event List (FAL), refer to Appendix C. This is a list of adverse events related to the ArcticLine Catheter or procedure that may be experienced by subjects. This list may help to assess if an adverse event is unexpected in nature. Additionally, refer to Appendix D, for expanded definitions on a subset of adverse events as they relate to endpoint assessment.

For emergency contact regarding a SAE, contact a clinical study representative immediately (refer to the study sponsor per the sponsor contact information).

Adverse Events and Deaths will be classified according to the standard definitions as outlined in Table 8.

All subject deaths must be reported by the Investigator to Medtronic on an adverse event eCRF (AE with outcome of fatal) as soon as possible after the Investigator first learns of the death. There should be one AE with the outcome of fatal.

A copy of the death certificate, if available, and allowed by state/local law, should be sent to the Medtronic clinical study team. When a death occurs in a hospital, a copy of the death summary report and all relevant hospital records should be sent to the Medtronic clinical study team, if available. If an autopsy is conducted, the autopsy report should also be sent to the Medtronic clinical study team if available and allowed by state/local law. When the death occurs at a remote center, 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 and/or procedure
- Death summary/hospital records (if available and allowed by state/local law)
- Autopsy report (if available and allowed by state/local law)
- Death certificate (if available and/or allowed by state/local law)

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:

- Cardiac Death: A death directly related to the electrical or mechanical dysfunction of the heart.

- Sudden Cardiac Death (SCD): Natural death due to cardiac causes, indicated 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.
- Non-cardiac Death: A death not classified as a cardiac death.
- Unknown Classification: Unknown death classification is intended for use only when there is insufficient or inadequate information to classify the death.

The CEC will review deaths and provide a final adjudication of the primary cause of death and cardiac classification. Regulatory reporting of Subject Deaths will be completed according to local regulatory requirements.

Table 7: Adverse Event Reporting Requirements

Serious Adverse Events (SAEs)	
Investigator submit to:	
Medtronic	**All geographies:** Report, without unjustified delay, all serious adverse events.
IRB/REB/MEC	**All geographies:** Submit per local reporting requirement.
Regulatory Authorities	**All geographies:** Submit per local reporting requirement.
Sponsor submit to:	
IRB/REB/MEC	**All geographies:** Submit per local reporting requirement.
Regulatory Authorities	**All geographies:** Submit per local reporting requirement.
Serious Adverse Device Effects (SADEs)	
Investigator submit to:	
Medtronic	**All geographies:** Submit as soon as possible after the Investigator first learns of the event, and per local requirements **Canada:** SADEs on the patient, the user or any other person must be reported to the Regulator and to the Sponsor within **72 hours** after it comes to the attention of the qualified investigator.
IRB/REB/MEC	**All geographies:** Submit per local reporting requirement.
Regulatory authorities	**All geographies:** Submit as soon as possible after the Investigator first learns of the event, and per local requirements
Sponsor submit to:	
IRB/REB/MEC	**All geographies:** Submit per local reporting requirement.

Regulatory authorities	**Canada**: All SADEs on the patient, the user or any other person: these must be reported by Medtronic within 10 days from the date the first person becomes aware. Preliminary and final reporting to the Canadian Ministry of Health (Health Canada) of events occurring inside (always) or outside Canada (in case of corrective actions) that is related to a failure of the device or a deterioration in its effectiveness, or any inadequacy in its labeling or its directions for use and 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. Report a) within 10 days after awareness, if incident has led to death or a serious deterioration in the state of health of a patient, user or other person b) within 30 days, if incident has not led to death or a serious deterioration in the state of health of a patient, user or other person, but could do so were it to recur c) as soon as possible, if incident occurred outside of Canada and is related to a corrective action. (Medical Devices Regulation Mandatory Problem Reporting 59(1), 59(2), 60 (1)) **All geographies:** Submit per local reporting requirement.
Unanticipated Adverse Device Effects (UADEs) and Unanticipated Serious Adverse Device Effects (USADEs)	
Investigator submit to:	
Medtronic	**US:** Submit as soon as possible, but no later than within 10 working days after the Investigator first learns of the event. (21 CFR 812.150(a)(1)) **Canada:** USADEs on the patient, the user or any other person must be reported to the Regulator and to the Sponsor within **72 hours** after it comes to the attention of the qualified investigator.
IRB/REB/MEC	**US:** Submit as soon as possible, but no later than within 10 working days after the Investigator first learns of the event. (21 CFR 812.150(a)(1)) **All geographies:** Submit per local reporting requirement.
Sponsor submit to	
Investigator	**All geographies:** Notification as soon as possible and not later than 10 working days after the sponsor first learns of the effect. (21 CFR 812.150(b)(1))
IRB/REB/MEC	**All geographies:** Notification as soon as possible and not later than 10 working days after the sponsor first learns of the effect. (21 CFR 812.150(b)(1))
Regulatory authorities	**US:** Notification as soon as possible to FDA, but not later than 10 working days after the sponsor first learns of the effect. (21 CFR 812.150(b)(1)) **Canada:** All USADEs on the patient, the user or any other person; these must be reported by Medtronic within 10 days from the first person at Medtronic that becomes aware. Preliminary and final reporting to the Canadian Ministry of Health (Health Canada) of events occurring inside (always) or outside Canada (in case of corrective actions) that is related to a failure of the device or a deterioration in its effectiveness, or any inadequacy in its labeling or its directions for use and 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. Report a) within 10 days after awareness, if incident has led to death or a serious deterioration in the state of health of a patient, user or other person b) within 30 days, if incident has not led to death or a serious deterioration in the state of health of a patient, user or other person, but could do so were it to recur c) as soon as possible, if incident occurred outside of Canada and is related to a corrective action. (Canada Medical Devices Regulations, SOR/98-282; Mandatory Problem Reporting 59(1), 59(2), 60 (1))

Adverse Device Effects	
Investigator submit to:	
Medtronic	**All geographies:** Submit in a timely manner after the Investigator first learns of the effect.
IRB/REB/MEC	**All geographies:** Submit per local reporting requirement.
Regulatory authorities	**All geographies:** Submit per local reporting requirement.
Sponsor submit to:	
IRB/REB/MEC	**All geographies:** Submit per local reporting requirement.
Regulatory authorities	**All geographies:** Submit per local reporting requirement.
All other reportable Adverse Events	
Investigator submit to:	
Medtronic	**All geographies:** Submit in a timely manner after the Investigator first learns of the event.
Regulatory authorities	**All geographies:** Submit per local reporting requirement.
IRB/REB/MEC	**All geographies:** Submit per local reporting requirement.
Sponsor submit to:	
Regulatory authorities	**All other geographies:** Submit per local reporting requirement.

Table 8: Adverse Event Classification Responsibilities

What is classified?	Who classifies?	Classification Parameters
Relatedness	Investigator	Procedure related, System related, Cardiovascular related
	Sponsor	Procedure related, System related
Seriousness	Investigator	SAE
	Sponsor	SAE, UADE/USADE, Device Deficiency with SADE potential
Diagnosis	Investigator	Based on presenting signs and symptoms and other supporting data
	Sponsor	MedDRA term assigned based on the data provided by Investigator
Death Classification	Investigator	Sudden Cardiac, Non-Sudden Cardiac, Non-Cardiac, Unknown

10.4. Reporting of Device Deficiencies

Device deficiency (DD) information will be collected throughout the study and are to be reported to Medtronic, as per Table 9: Device Deficiency Reporting Requirements. A Medtronic representative will review the device deficiency for completeness and accuracy and when necessary will request clarification and/or additional information from the Investigator. Note that device deficiencies that result in an adverse device effect (ADE) to the subject should be captured as an Adverse Event only.

Device deficiencies that did not lead to an AE, but could have led to a Serious Adverse Device Effect (SADE) (i.e., if suitable action had not been taken, if intervention had not been made, or if the circumstances had been less fortunate) require immediate reporting. For device deficiencies that require immediate reporting, initial reporting may be done by contacting the study sponsor per the sponsor contact information.

Table 9: Device Deficiency Reporting Requirements

Device Deficiencies and SADE Potential	
Investigator submit to:	
Medtronic	**All geographies:** Report, without unjustified delay, all device deficiencies that could have led to a serious adverse device effect
Regulatory authorities	**All geographies:** Submit per local reporting requirement.
IRB/REB/MEC	**All geographies:** Submit per local reporting requirement.
Sponsor submit to:	
IRB/REB/MEC	**All geographies:** Submit per local reporting requirement.
Regulatory authorities	**Canada:** Any Device Deficiency that: • has resulted in any of the consequences characteristic of an SAE on the patient, the user or any other person; These must be reported by Medtronic within 10 days from the date Medtronic becomes aware. or • could do so were it to reoccur. These must be reported by Medtronic within 30 days from the date Medtronic becomes aware. Preliminary and final reporting to the Canadian Ministry of Health (Health Canada) of events occurring inside (always) or outside Canada (in case of corrective actions) that is related to a failure of the device or a deterioration in its effectiveness, or any inadequacy in its labeling or its directions for use and 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. Report a) within 10 days after awareness, if incident has led to death or a serious deterioration in the state of health of a patient, user or other person b) within 30 days, if incident has not led to death or a serious deterioration in the state of health of a patient, user or other person, but could do so were it to recur c) as soon as possible, if incident occurred outside of Canada and is related to a corrective action. (Canada Medical Devices Regulations, SOR/98-282; Mandatory Problem Reporting 59(1), 59(2), 60 (1)).

	All geographies: Submit per local reporting requirement.
All Other Device Deficiencies	
Investigator submit to:	
Medtronic	**All geographies:** Submit in a timely manner after the Investigator first learns of the event.
IRB/REB/MEC	**All geographies:** Submit per local reporting requirement.
Regulatory authorities	**All geographies:** Submit per local reporting requirement.

10.5. Reporting of Product Complaints

In geographies where devices are market-released, product complaint reporting is applicable. This includes when an AE is related to a market-released device during the study. The reporting of product complaints is not part of the Study and should be done in addition to the Adverse Event reporting requirements. Refer to local regulations for reporting requirements.

Product Complaint: Any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a medical device that has been placed on the market.

It is the responsibility of the Investigator to report all product complaint(s) associated with a market-released medical device distributed by Medtronic, regardless whether they are related to intended use, misuse or abuse of the product. Reporting must be performed immediately and via the regular channels for market-released products.

Medtronic will notify the regulatory authorities (e.g. FDA, Health Canada) as applicable for the following incidents immediately upon learning of them:

- Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or instructions for use which led or might have led to the death or serious deterioration in the state of health of a patient, user, or other person.
- Any technical or medical reason resulting in withdrawal of a device from the market by the manufacturer.
- A serious deterioration in the state of heath includes:
    - Life-threatening illness or injury
    - Permanent impairment of a body function or permanent damage to a body structure
    - A condition necessitating medical or surgical intervention to prevent permanent impairment of a body function or permanent damage to a body structure

11. Clinical Events Committee

An independent Clinical Events Committee (CEC) will review and adjudicate all adverse events as well as all deaths for subjects participating in the study.

The CEC will consist of a minimum of three (3) non-Medtronic employed physicians that are not participating Investigators for the study, including a CEC chairperson. Medtronic personnel may facilitate and participate in a CEC meeting but will be non-voting members.

For adverse events and deaths reviewed by the CEC, Medtronic will provide the CEC with the Investigator's description and classification. The CEC is responsible for reviewing the Investigator's assessment and supportive documentation (when available), reviewing applicable definitions, and determining final classifications for all adjudication parameters. Additionally, the CEC will provide an adjudication of the death classification for all reported deaths including primary cause of death and cardiac classification.

If the CEC disagrees with the Investigator's classification of the event, the rationale will be provided to the Investigator. If the Investigator agrees with the CEC's adjudication, the eCRF documenting the event will be updated accordingly.

If the Investigator does not agree with the CEC's adjudication classification, both determinations will be provided within the final report; however, the CEC's adjudication will be used for data analysis. The disagreement will also be included in reporting to IRB/REB/MECs and regulatory authorities, if required.

12. Statistical Design and Methods

A separate Statistical Analysis Plan (SAP) will be developed to further describe statistical methods, pre-specified data handling rules, and pre-specified analyses that will be included in study reports. Any deviation from the pre-specified statistical analyses will be noted in the study report.

Additional exploratory analyses of the data may be conducted as deemed appropriate.

As this is a feasibility study, analysis of accruing data will be allowed. Analyses are planned at the following time points (though only select objectives may be analyzed at the first 2 analyses):

- After completion of the first 10 subject index procedures and 1 week follow-up visit
- After completion of all 30 subject index procedures and 1 week follow-up visit
- After completion of all subject follow-up visits through 12 month follow-up visit

12.1. Primary Objective

Estimate the incidence of ArcticLine Catheter-related and ArcticLine cryoablation procedure-related serious adverse events (SAEs) with an onset date within 7 days post-procedure.

Endpoint Definition

ArcticLine Catheter-related or ArcticLine cryoablation procedure-related SAEs, with an onset date within 7 days post-procedure, as adjudicated by the Clinical Events Committee (CEC), described as follows:

- Atrioesophageal fistula
- Cardiac perforation/tamponade
- Cerebrovascular accident
- Death
- Esophageal injury
- Major bleeding
- Myocardial infarction
- Pericarditis
- Phrenic nerve injury (ongoing at hospital discharge)
- Transient ischemic attack
- Vagal nerve injury resulting in esophageal dysmotility or gastroparesis
- Vascular access complications

Sample Size

The sample size of 30 treated subjects for this study was chosen with the goal to collect preliminary safety and effectiveness data on the ArcticLine Catheter's use in both the left and right atrium. Assuming there are 30 ArcticLine cryoablation procedures in the study and the SAE rate is 3.3% (1/30 subjects: the rate of cryoablation procedure events in the STOP AF pivotal trial [PMA #P100010] was 3.1%), the exact 95% confidence interval will have a width of 17%.

Analysis Methods

The percentage of catheter related and cryoablation procedure related SAEs will be calculated as the number of procedures with at least one SAE meeting the endpoint definition divided by the number of cryoablation procedures. Each procedure will count, so subjects with repeat cryoablations will contribute more than once to the denominator. Exact methods will be used to construct a 95% confidence interval for the percentage of procedures with an SAE.

Determination of Patients for Analysis

All ArcticLine cryoablation procedures will be included. An ArcticLine cryoablation procedure is considered to have occurred once the ArcticLine Catheter is introduced into the vasculature.

12.2. Ancillary Objective #1

Estimate the percentage of patients with acute treatment success of the ArcticLine Catheter at the left atrial roof and posterior wall in patients with demonstrated entrance block of all pulmonary veins and who underwent roof and posterior wall ablation with ArcticLine.

Endpoint Definition

Subjects must have confirmed block at the roof line and posterior wall line ("roof/wall") via periprocedural assessment of posterior wall isolation at the completion of the cryoablation procedure to be considered an acute treatment success.

Analysis Methods

The percentage of acute roof/wall treatment successes will be calculated as the number of roof/wall procedures achieving success divided by the number of index ArcticLine cryoablation procedures where the roof/wall was attempted. Exact methods will be used to construct a 95% confidence interval for the percentage.

Determination of Patients for Analysis

All subjects undergoing an ArcticLine cryoablation procedure of the roof/wall will be included. An ArcticLine cryoablation procedure of the roof/wall is considered to have occurred once an ArcticLine cryoapplication at the roof and/or wall begins. Only the first ArcticLine cryoablation procedure of the roof/wall per subject will be included.

12.3. Ancillary Objective #2

Estimate the percentage of patients with acute treatment success of the ArcticLine Catheter at the mitral isthmus in patients who underwent mitral isthmus ablation with ArcticLine.

Endpoint Definition

Subjects must have confirmed bi-directional conduction block at the mitral isthmus line via periprocedural assessment at the completion of the cryoablation procedure to be considered an acute treatment success.

Analysis Methods

The percentage of acute mitral isthmus line treatment successes will be calculated as the number of mitral isthmus line procedures achieving success divided by the number of index ArcticLine cryoablation procedures where the mitral isthmus line was attempted. Exact methods will be used to construct a 95% confidence interval for the percentage.

Determination of Patients for Analysis

All subjects undergoing an ArcticLine cryoablation procedure of the mitral isthmus will be included. An ArcticLine cryoablation procedure of the mitral isthmus is considered to have occurred once an ArcticLine cryoapplication at the mitral isthmus begins. Only the first ArcticLine cryoablation procedure of the mitral isthmus per subject will be included.

12.4. Ancillary Objective #3

Estimate the percentage of patients with acute treatment success of the ArcticLine Catheter at the CTI in patients who underwent CTI ablation with ArcticLine.

Endpoint Definition

Subjects must have confirmed bi-directional conduction block at the CTI line via periprocedural assessment at the completion of the cryoablation procedure to be considered an acute treatment success.

Analysis Methods

The percentage of acute CTI line treatment successes will be calculated as the number of CTI line procedures achieving success divided by the number of index ArcticLine cryoablation procedures where the CTI line was attempted. Exact methods will be used to construct a 95% confidence interval for the percentage.

Determination of Patients for Analysis

All subjects undergoing an ArcticLine cryoablation procedure of the CTI will be included. An ArcticLine cryoablation procedure of the CTI is considered to have occurred once an ArcticLine cryoapplication at the CTI begins. Only the first ArcticLine cryoablation procedure of the CTI per subject will be included.

12.5. Ancillary Objective #4

Characterize chronic treatment success of the ArcticLine Catheter in patients with demonstrated entrance block of all pulmonary veins.

Endpoint Definition

AF/AFL/AT episodes of at least 30 seconds duration from the end of the 90 day blanking period through the 12 month visit.

Analysis Methods

Standard statistics will be used to summarize the percentage of patients without AF/AFL/AT and cumulative time spent in AF/AFL/AT as collected from the 12 month Holter data.

Determination of Patients for Analysis

- All subjects undergoing an ArcticLine cryoablation procedure and who meet the following criteria will be included in the analysis:
    - Confirmed acute entrance block of all pulmonary veins
    - Confirmed acute posterior wall isolation (i.e. roof line and posterior wall line conduction block)
    - Confirmed acute bi-directional conduction block at the mitral isthmus, if applicable
    - Available 12 month Holter data
- Note: An ArcticLine cryoablation procedure is considered to have occurred once the ArcticLine Catheter is introduced into the vasculature.
- Note: For subjects who did not receive CTI ablation with ArcticLine Catheter, documented occurrence and treatment of typical right-sided cavotricuspid isthmus dependent atrial flutter during follow-up will not contribute to this endpoint if confirmed by entrainment maneuvers during EP testing.

12.6. Ancillary Objective #5

Estimate the incidence of ArcticLine Catheter-related and ArcticLine cryoablation procedure-related serious adverse events (SAE) through the 12 month visit.

Endpoint Definition

ArcticLine Catheter-related or ArcticLine cryoablation procedure-related SAEs, as adjudicated by the Clinical Events Committee (CEC).

Analysis Methods

Kaplan-Meier methods will be used to estimate event percentages separately for each of the events listed above. Time 0 will be the time of the index ablation and subjects without an event will be censored at their last documented time in the study (e.g., follow-up, exit, death). Though Kaplan-Meier methods will be used, only point estimates for the rates at 12 months (not graphs) will be reported.

Determination of Patients for Analysis

All subjects undergoing an ArcticLine cryoablation procedure will be included. An ArcticLine cryoablation procedure is considered to have occurred once the ArcticLine Catheter is introduced into the vasculature.

12.7. Ancillary Objective #6

Characterize procedural data:

- Total procedure time
- Total ArcticLine Catheter use time
- Left atrial dwell time
- Total fluoroscopy time
- Total fluoroscopy time during ArcticLine Catheter use
- Application duration
- Number of applications
- Fluoroscopy dose

Endpoint Definition

- Total procedure time is defined as time from first venous access to time of last catheter removal.
- Total ArcticLine Catheter use time is defined as cumulative time from each introduction of ArcticLine Catheter into the body to its removal.
- Left atrial dwell time is defined as time from transseptal puncture to time of removal of last sheath/catheter from the left atrium.
- Total fluoroscopy time is defined as total fluoroscopy time used during the procedure.
- Total fluoroscopy time during ArcticLine Catheter use is defined as the cumulative fluoroscopy time from each introduction of ArcticLine Catheter into the body to its removal.
- Application duration is defined as total duration in which cryoablation from the ArcticLine Catheter is applied to cardiac tissue overall and individually to each target area.
- Number of applications is defined as the total number of times in which the ArcticLine Catheter was used to ablate cardiac tissue overall and individually to each target area.
- Total fluoroscopy dose is defined as the amount of radiation deposited into the tissue, measured in Gy or mGy units.

Analysis Methods

Standard statistics (e.g., mean, standard deviation) will be used to summarize each variable. Data from index cryoablations and repeat cryoablations will be reported separately.

Determination of Patients for Analysis

All subjects undergoing a cryoablation procedure will be included. A cryoablation procedure is considered to have occurred once the skin is punctured.

12.8. Ancillary Objective #7

Estimate the incidence of adverse events (AEs) through the 12 month visit.

Endpoint Definition

Characterize adverse events through the 12 month visit, described as follows:

- Atrioesophageal fistula
- Cardiac perforation/tamponade
- Cerebrovascular accident
- Coronary artery spasm
- Death
- Esophageal injury
- Lung injury (including hemoptysis)
- Major bleeding
- Myocardial infarction
- Pericarditis
- Phrenic nerve injury (ongoing from hospital discharge)
- Pulmonary vein stenosis
- Symptomatic persistent iatrogenic atrial septal defect
- Transient ischemic attack
- Vagal nerve injury
- Vascular access complications

Analysis Methods

Kaplan-Meier methods will be used to estimate event percentages. Time 0 will be the time of the index ablation and subjects without an event will be censored at their last documented time in the study (e.g., follow-up, exit, death). Though Kaplan-Meier methods will be used, only point estimates for the percentages at 12 months (not graphs) will be reported.

Determination of Patients for Analysis

All subjects undergoing an ArcticLine cryoablation procedure will be included. A cryoablation procedure is considered to have occurred once the skin is punctured.

13. Ethics

13.1. Statement(s) of Compliance

The study will be conducted in compliance with international ethical and scientific quality standards, known as good clinical practice (GCP). GCP includes review and approval by an independent IRB/REB/MEC before initiating a study, continuing review of an ongoing study by an IRB/REB/MEC, and obtaining and documenting the freely given informed consent of a subject before initiating the study.

The study will be conducted according to federal, national and local laws, regulations, standards, and requirements of the countries/geographies where the study is being conducted. For all geographies, the principles of the Declaration of Helsinki have been implemented through the patient informed consent (IC) process, IRB/REB/MEC approval, study training, clinical trial registration, preclinical testing, risk-benefit assessment and publication policy.

All geographies will follow and comply with:

- Principles of Declaration of Helsinki (including privacy and data protection laws), or the laws and regulations of each participating country, whichever affords greater protection for the study subjects
- 21 CFR Part 11 (Electronic Records, Electronic Signatures)
- The procedures described within this CIP
- Local IRB/REB/MEC requirements

All participating geographies will make study data available to the regulatory body such as FDA or Health Canada if the regulatory body deems an onsite inspection necessary. The regulatory body will be able to inspect records at clinical centers around the world to resolve any uncertainties about whether the study was conducted in accordance with good clinical practice.

In addition to the regulatory requirements outlined above, the study will be conducted in compliance with relevant local laws. These include but are not limited to:

- In Canada, the Medical Devices Regulations, 1998 (SOR/98-282), 59(1), 59(2), 60(1), and the Canadian Regulatory Guidelines for Mandatory Medical Device Problem Reporting for Medical Devices, 2011.
- Declaration of Helsinki 2013
- In the United States and Canada, US FDA 21 CFR Parts
    - 50: Protection of Human Subjects
    - 56: Institutional Review Boards
    - 812: Investigational Device Exemptions

The study will be publicly registered prior to first enrollment in accordance with the 2007 Food and Drug Administration Amendments Act (FDAAA) and Declaration of Helsinki on http://clinicaltrials.gov (PL 110-85, Section 810(a)).

Approval of the Clinical Investigation Plan (CIP) is required from the following groups prior to any study procedures at a study center:

- Health Canada or FDA
- Medtronic
- Principal Investigators (where required by local law)
- An independent IRB/REB/MEC

14. Study Administration

14.1. Monitoring

It is the responsibility of Medtronic to ensure proper monitoring of this clinical study. Trained Medtronic personnel or delegates appointed by Medtronic may perform study monitoring at the study center to ensure that the study is conducted in accordance with the CIP, the Clinical Trial Agreement, and applicable regulatory and local requirements. Medtronic, or delegates, must therefore be allowed access to the subjects' case histories (clinic and hospital records, and other source data/documentation) upon request as per the IC Form, Research Authorization (where applicable) and Clinical Trial Agreement. The Principal Investigator should also be available during monitoring visits.

Frequency of monitoring visits may be based upon subject enrollment, duration of the study, study compliance, number of adverse events, number of deviations, findings from previous monitoring visits and any suspected inconsistency in data that requires investigation. Regulatory documents may be reviewed at each study center. Monitoring for the study may include, but not limited to, site qualification visits, site initiation visits, interim monitoring visits, and closeout visits, will be done in accordance to the study-specific monitoring plan.

Monitoring visits may be conducted periodically to assess center study progress, the Investigator's adherence to the CIP, regulatory compliance including but not limited to IRB/REB/MEC approval and review of the study, maintenance of records and reports, and review of source documents against subject eCRFs. Monitors review center regulatory and study compliance by identifying findings of non-compliance and communicating those findings along with recommendations for preventative/corrective actions to center personnel. Monitors may work with study personnel to determine appropriate corrective action recommendations and to identify trends within the study or at a center.

14.2. Data Management

Data will be collected using an electronic data management system for clinical studies. eCRF 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.

Data collected by Holters, Patient Activated Ambulatory Monitors and ECGs will be managed and over-read by a core lab. Final classification of recurrent AF/AT/AFL will be stored in the study database.

Study management reports may be generated to assess data quality and study progress. At the end of the study, the data will be frozen and will be retained indefinitely by Medtronic.

All records and other information about subjects participating in the study will be treated as confidential. Data will be transferred and processed by Medtronic or a third party designated by Medtronic in a key coded form, unless it's impossible to make it anonymous, for instance, where the subject's name cannot be removed from the data carrier, such as fluoroscopy images. In the case that de-identifying is impossible or involves a disproportionate effort, files containing personal data of subjects shall only be made accessible to authorized persons (secured role-based access).

Procedures in the CIP require source documentation. Source documentation will be maintained at the center. Source documents, which may include worksheets, subject medical records, console files, must be created and maintained by the investigational center team.

The data reported on the eCRFs shall be derived from source documents and be consistent with these source documents, and any discrepancies shall be explained in writing. The eCRF may be considered source for the following data collection elements:

- Database generated subject reference ID
- Esophageal temperature
- Investigator assessment of adverse event or death relatedness and severity
- Date center became aware of the adverse event, device deficiency or death
- Reason for study deviation
- If Arctic Front Advance and Achieve/Achieve Advance is used, time of isolation of the cryoablation catheter
- Investigator's assessment of conduction block

When copies or print-outs of the source documents are made, center personnel must ensure that all copies or printouts of the original source documents are certified copies.

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

14.3. Confidentiality

All records and other information about subjects participating in the study will be treated as confidential.

14.4. Liability

If used, warranty information is provided in the product packaging for the AFA, Freezor MAX and sheath devices.

Canada: Medtronic of Canada is a wholly owned subsidiary of Medtronic, Inc., which as the parent company of such entity maintains appropriate general liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a General Liability insurance statement/certificate will be provided to the REB/MEC.

US: Medtronic Inc. maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable law and custom concerning specific insurance coverage. If required, a Clinical Trial Insurance statement/certificate will be provided to the IRB.

The study is conducted in multiple countries; therefore, reimbursement and indemnification will be addressed on a country specific basis in the study documents and center Clinical Trial Agreements.

14.5. CIP Amendments

Approval of subsequent revisions to the CIP is required at each study center from the following groups prior to implementation of the revised CIP at the center:

- Medtronic
- Principal Investigators (where required by local law)
- Geography-specific regulatory authorities (if regulatory approval is required)
- An independent IRB/REB/MEC

If a CIP amendment occurs, center personnel will need to be re-trained as necessary, and will need to submit any changes to their IRB/REB/MEC as required by the committee.

14.6. Record Retention and Reports

Medtronic records and reports will be maintained in a password-protected document management system, and paper documents (where applicable) will be stored in stored in secured file cabinets at Medtronic during the course of this study. After closure of the study Medtronic will archive records and reports indefinitely.

Investigator Records

The Investigator is responsible for the preparation and retention of the records cited below. All the below records, except for case history records and eCRFs, should be kept in the Investigator Site File (i.e., the study binder provided to the Investigator) or Subject Study Binder. CRFs must be maintained and signed electronically within the electronic data capture system during the study.

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 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/REB/MEC, sponsor, monitor, local regulatory agencies and the Investigator that pertains to the investigation, including required reports
- Subject's case history records, including:
- IC Form signed and dated by subject
- Observations of adverse events and device deficiencies
- Medical history
- Procedure and follow-up data
- Documentation of the dates and rationale for any deviation from the CIP
- Reports of adverse events
- Subject screening logs (if used)
- List of investigation centers
- Financial disclosure of Investigators
- Device Disposition Logs
- All approved versions of the CIP, IC, and Investigator's Brochure/Report of Prior Investigations
- Signed and dated Clinical Trial Agreement and Investigator Statement
- Current curriculum vitae of Investigators
- Documentation of delegated tasks
- IRB/REB/MEC approval documentation. Written information that the Investigator or other study staff, when member of the IRB/REB/MEC, did not participate in the approval process.

Approval documentation must include the IRB/REB/MEC composition, where required per local law.

- Regulatory authority notification, correspondence and approval, where required per local law
- Study training records for center staff
- Insurance certificates (where requested by the IRB/REB/MEC)
- Any other records that FDA and local regulatory agencies require to be maintained
- Final Study Report including the statistical analysis

Investigator Reports

The Investigator is responsible for the preparation (review and signature) and submission to the sponsor of all case report forms, adverse events, device deficiencies, deaths, and any deviations from the clinical investigation plan. If any action is taken by an IRB/EC 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.

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

Table 10: Investigator reports applicable for all geographies per Medtronic requirements

Report	Submit to	Description/Constraints
Withdrawal of IRB/EC approval	Sponsor and Relevant authorities	The Investigator must report a withdrawal of approval by the reviewing IRB/EC of the Investigator's part of the investigation within 5 working days.
Study deviations	Sponsor and IRB/EC	Any deviation from the clinical investigation plan shall be recorded together with the explanation of the deviation. Notice of deviations from the CIP to protect the life or physical wellbeing 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.

Report	Submit to	Description/Constraints
Final report	Sponsor, IRBs/ECs, and Relevant Authorities	This report must be submitted within 3 months of study completion or termination.
Refer to Section 10 for adverse event, complaint, and device deficiency reporting.		

Table 11: Additional Investigator reports applicable to the United States

Report	Submit to	Description/Constraints
Withdrawal of IRB/EC approval	Sponsor	The Investigator must report a withdrawal of approval by the reviewing IRB/EC of the Investigator's part of the investigation within 5 working days. (21 CRF 812.150 (a)(2)).
Progress report	Sponsor and IRB/EC	The Investigator must submit this report to the sponsor and IRB at regular intervals, but in no event less than yearly. (21 CFR 812.150 (a)(3)).
Study deviations	Sponsor and IRB/EC	Notice of deviations from the clinical investigation plan to protect the life or physical wellbeing 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/EC, 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	Sponsor and IRBs/ECs	If an Investigator uses a device without obtaining a signed Informed Consent Form, the Investigator

Report	Submit to	Description/Constraints
Consent Form prior to investigational device use		shall report such use within 5 working days after device use. (21 CFR 812.150(a)(5))
Final report	Sponsor, IRBs/ECs, and 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))

Sponsor Records

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

- All correspondence which pertains to the investigation
- Signed Investigator Trial Agreements, financialdisclosureofInvestigators,andcurrent signedanddated(Europeonly)curriculum vitae of Principal Investigator and key members of the investigator center team (as required by local law), and Delegated Tasks List
- All approved versions of the ICF, and other information provided to the subjects and advertisements, including translations.
- All approved versions of the Clinical Investigation Plan and study related reports, Investigator's Brochure/Report of Prior Investigation Summary
- All case report forms and supporting documentation submitted by investigator, samples of Informed Consent Forms, and other information provided to the subjects
- Copies of all IRB/EC approval letters and relevant IRB/EC correspondence and IRB/EC voting list/roster/letter of assurance
- Names of the institutions in which the clinical investigation will be conducted
- Regulatory authorities correspondence, notification and approval, as required by national legislation
- Insurance certificates
- Names/contact addresses of monitors
- Monitoring visit reports and follow-up letters
- Forms for reporting any adverse events and adverse device effects
- Statistical analyses and underlying supporting data.
- Final report of the clinical investigation
- Study training records for center personnel and Medtronic personnel involved in the study
- Any other records that local regulatory agencies require to be maintained

Sponsor Reports

Medtronic shall prepare and submit the following complete, accurate, and timely reports listed in the table below. In addition to the reports listed below, Medtronic shall, upon request of reviewing IRB/EC, regulatory agency or FDA, provide accurate, complete and current information about any aspect of the investigation. Safety data reporting requirements are listed in the adverse event section.

Table 12: Sponsor reports for the United States

Report	Submit to	Description/Constraints
Withdrawal of IRB/EC approval	Investigators, IRB/EC, FDA, and relevant authorities	Notification within five working days. (21 CFR 812.150(b)(2))
Withdrawal of FDA approval	Investigators, IRB/EC, and relevant authorities	Notification within 5 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/EC and FDA	Progress reports will be submitted at least annually. (21 CFR 812.150(b)(5), 812.36(f)
Recall and device disposition	Investigators, Head of Institution, IRB/EC, relevant authorities, and 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))

Report	Submit to	Description/Constraints
Failure to obtain Informed Consent Form	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/EC, 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 within 6 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. Site specific study deviations will be submitted to investigators periodically.
Other	IRB/EC, and FDA	Accurate, complete, and current information about any aspect of the investigation. (21 CFR 812.150(b)(10))

Table 13: Sponsor reports for Canada

Report	Submit to	Description/Constraints
Premature termination or suspension of the clinical investigation	Investigators, Ethics Committee, Relevant authorities, and Head of the Institution	Provide prompt notification of termination or suspension and reason(s).
Recall and device disposition	Investigators, Ethics Committee	Notification within 30 working days and will include the reasons for any request that an investigator return, repair, or otherwise dispose of any devices.
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. Site specific study deviations will be submitted to investigators periodically.

14.7. Publication and Use of Information

Publications from the study will be handled according to Medtronic Global Standard Operating Procedures and as indicated in the Clinical Trial Agreement.

Publication Committee

Medtronic may form the ArcticLine Feasibility Study Publication Committee from the study Investigators. Medtronic personnel may serve as members of the committee. This committee will manage study publications with the goal of publishing findings from the data. The Publication Committee will develop the final Publication Plan as a separate document.

The Publication Committee's role is to: 1) manage elements addressed in the publication plan as outlined in this section, 2) develop the final Publication Plan under separate cover, 3) execute the Publication Plan, 4) oversee the publication of primary and ancillary study results, 5) review and prioritize publication proposals, 6) provide input on publication content, and 7) determine authorship. In addition, the committee will apply and reinforce the authorship guidelines set forth in the Publication Plan.

Membership in the Publication Committee does not guarantee authorship. The committee will meet as needed.

Management of Primary and Ancillary Publications

The Publication Committee reviews, prioritizes, and manages all publications including primary and ancillary publications. Primary publications are those that address analyses of the primary objective and ancillary objectives as specified in the CIP. An ancillary publication is any publication that does not address the study objectives identified in the CIP. They include publications proposed and developed by other Medtronic departments or entities, clinicians participating in this clinical study, and clinicians not participating in this clinical study. The committee will work with Medtronic to ensure that requests do not present conflicts with other proposals, are not duplicative, and to determine which ancillary publication proposals, if any, will be supported.

The committee may decide that no publications, including abstracts, will be published prior to the end of the study or with individual center data. Requests for publications on study objectives utilizing subset data (e.g., regional) will be evaluated for scientific validity and the ability of Medtronic to provide resources.

Criteria for Determining Authorship

Publications will adhere to authorship criteria defined by the International Committee of Medical Journal Editors (ICMJE, Uniform requirements for manuscripts submitted to biomedical journals,

www.icmje.org). Individual authorship criteria defined by the target journal or conference will be followed when it differs from ICMJE criteria.

Authors, including Medtronic personnel, must at a minimum meet all the conditions below:

- Substantial contribution to conception and design, or acquisition of data, or analysis and interpretation of data
- Drafting the article or revising it critically for important intellectual content
- Final approval of the version to be published
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Decisions regarding authorship and contributorship will be made by the committee. The selected authors will be responsible for drafting the publication. All selected authors must fulfill the authorship conditions stated above to be listed as authors, and all contributors who fulfill the conditions must be listed as authors.

All Investigators not listed as co-authors will be acknowledged as the "Medtronic ArcticLine Feasibility Study Investigators" and will be individually listed according to the guidelines of the applicable scientific journal when possible and affiliation. Any other contributors will be acknowledged by name with their specific contribution indicated.

Transparency

Transparency of study results will be maintained by the following means:

- a final report, describing the results of all objectives and analysis, will be distributed to all Investigators and IRB/REB/MECs of participating countries when required by local law
- registering and posting the study results on ClinicalTrials.gov based on the posting rules stipulated
- submitting for publication the primary study results after the study ends
- disclosing conflicts of interest (e.g., financial) of the co-authors of publications according to the policies set forth by the corresponding journals and conferences
- making an individual center's study data accessible to the corresponding Investigator after the completion of the study, if requested.

14.8. Suspension or Early Termination

14.8.1. Early Termination or Suspension

Early termination is the closure of a clinical study that occurs prior to meeting defined endpoints. This is possible for the whole study or a single center. Suspension is a temporary postponement of study activities related to enrollment. This is possible for the whole study or a single center. If suspension is lifted, the Investigator shall assess whether to continue the clinical study at their center.

14.8.2. Study-Wide Termination or Suspension

Possible reasons for considering study suspension or termination of the study include but are not limited to:

- 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)
- Technical issues during the manufacturing process

14.8.3. Investigator/Center Termination or Suspension

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

- Failure to obtain IRB/REB/MEC annual renewal of the study
- Persistent non-compliance to the CIP (e.g. failure to adhere to inclusion/exclusion criteria, failure to follow subjects per visit schedule)
- 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 resolve data queries and monitoring findings in a timely manner)
- IRB/REB/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)

14.8.4. Procedures for Termination or Suspension

14.8.4.1. Medtronic-Initiated and Regulatory Authority-Initiated

- Medtronic will promptly inform the clinical Investigators of the termination or suspension and the reasons and inform the regulatory authority(ies) where required.
- In the case of study termination or suspension for reasons other than a temporary IRB/REB/MEC approval lapse, the Investigator will promptly inform the IRB/REB/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, subject enrollment must stop until the suspension is lifted by Medtronic.
- In the case of a study suspension, enrolled subjects should continue to be followed out of consideration of their safety, rights and welfare.

14.8.4.2. Investigator-Initiated

- The Investigator will 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/REB/MEC.
- The Investigator will promptly inform the regulatory authorities (where required per regulatory requirements).
- The Investigator will promptly inform the subjects and/or the personal physician of the subjects to ensure appropriate care and follow-up is provided.
- In the case of a study suspension, subjects enrolled should continue to be followed out of consideration of their safety, rights and welfare.

14.8.4.3. IRB/REB/MEC-Initiated

- The Investigator will inform Medtronic and provide a detailed written explanation of the termination or suspension within 5 business days.
- Subject enrollment must stop until the suspension is lifted.
- Subjects already enrolled should continue to be followed in accordance with IRB/REB/MEC policy or its determination if 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 (or legally-authorized designees as allowed by local law) and/or the personal physician of the subjects, with the rationale for the study termination or suspension.

- The Investigator will promptly inform the regulatory authorities (where required per regulatory requirements).

15. References

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- Winkle RA. How much ablation to eliminate atrial fibrillation: Is less more or is more more? Heart Rhythm. Epub ahead of print. DOI:http://dx.doi.org/10.1016/j.hrthm.2015.06.031
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16. Appendices

Appendix A: CryoConsole Investigational Label

CryoConsoles used in the study will have investigational software installed, a Catheter File, to allow for use of the ArcticLine Catheter. These CryoConsoles will have a console label affixed to the exterior that denotes the presence of investigational software. As the study will be conducted in both Canada and US, the label will be in both French and English and consist of the following language:

CAUTION / ATTENTION

CryoConsole 106A3
This CryoConsole is used for: ArcticLine Feasibility Study
Cette CryoConsole est utilisée pour l'étude clinique: ArcticLine Feasibility Study

One (1) Investigational ArcticLine Catheter File (software) installed.
(in addition to other, commercially available, software)
Un (1) fichier de recherche "ArcticLine Catheter File" (logiciel) installé.
(en plus d'autres logiciels commerciaux)

ArcticLine Catheter File:
Exclusively for clinical investigations / Exclusivement pour l'investigation clinique
To be used by qualified investigators only / Réservé uniquement à l'usage de chercheurs qual
CAUTION: Federal Law (USA) restricts this device to sale by or on the order of a physician.
CAUTION: Investigational Device. Limited by Federal Law (USA) to investigational use.

For questions, contact the Investigator:
En cas de questions, contacter le chercheur:

_____

See ArcticLine Instructions for Use for more details.
Voir les Instructions d'utilisation du cathéter ArcticLine pour plus d'information.

Medtronic CryoCath LP
9000 Autoroute Transcanadienne
Pointe-Claire, Quebec, H9R 5Z8
Canada

Appendix B: Instructions For Use

Always reference the current version of the Instructions For Use document as provided by Medtronic under separate cover.

Appendix C: Foreseeable Adverse Events

The information provided in this section pertains to foreseeable adverse events that may be observed in study subjects and may collectively assist in identifying those events for a given device or therapy that are unexpected in nature.

The cryoablation procedure involves surgery, therefore, standard adverse events associated with a surgical procedure may be experienced (e.g. anesthesia complications, injury, infections, bleeding, exacerbation of pre-existing conditions, healing complications). The focus of this section is to specifically address in mored etail, those events that are foreseeable due to the use, performance, and/or presence of the ArcticLine Catheter under investigation.

Treatment required for procedure and/or cryoablation system related adverse events that are experienced may include medication or other surgical and medical remedies. The adverse events associated with the use of the ArcticLine Catheter include but are not limited to those in Table 14.

Table 14 pertains to the foreseeable/anticipated adverse events that may be observed in the study and may assist in identifying those adverse events that are unexpected in nature.

Table 14: Foreseeable adverse events

Adverse Event/Risk	Definition
Access site complications (e.g. bruising, ecchymosis)	Complications at catheter insertion site in the groin
Anemia	Deficiency of red blood cells or of hemoglobin in the blood resulting in weariness
Anxiety	Feeling of worry, nervousness, or unease
Arrhythmia (e.g. atrial flutter, bradycardia, heart block, tachycardia)	Disruption of normal heart rate or rhythm
Back pain	Pain felt in the lower or upper back
Bleeding, possibly requiring transfusion	Loss of blood, including loss resulting in transfusion
Bronchitis	Inflammation of the lining of bronchial tubes that carry air to and from the lungs
Cardiac tamponade	Pressure on the heart as a result of fluid collecting in the sac surrounding the heart
Cardiopulmonary arrest	Cessation of blood circulation and/or respiration due to dysfunction of the heart and/or lungs
Catheter entrapment in cardiac structures requiring intervention	Tangling of the catheter in the heart which requires invasive intervention, including surgical repair
Cerebral vascular accident	Blockage of blood flow, or rupture of an artery, to the brain which causes sudden death of brain cells

Adverse Event/Risk	Definition
Chest discomfort/pain/pressure	Includes a range of feeling from sharp stabbing to dull ache in the chest
Cold feeling	Having a low or inadequate temperature
Coronary artery spasm	Temporary constriction of a coronary artery, including ECG evidence reflecting ST segment abnormally high above baseline
Cough	Rapid expulsion of air from the lungs
Death	Complication or deterioration of health ultimately leading to a patient's death
Diarrhea	Feces discharged from the bowels frequently and in a liquid form
Dizziness	Feeling faint, woozy, weak or unsteady
Embolism	Formation and dislodgement of a blood clot (thrombus) or dislodgement of cholesterol/plaque within the blood vessel, which travels downstream into small vessels, blocking blood flow and causing temporary or permanent damage to organs distal to blockage. Emboli are known to cause myocardial infarction, transient ischemic attack, stroke/cardiovascular accident, blurred vision, visual changes, paralysis, paresis, or kidney damage, peripheral ischemia and may ultimately lead to incapacitation or death. Symptomatic and non-symptomatic.
Esophageal damage (including atrioesophageal fistula)	Damage to the esophagus, including ulcer and atrioesophageal fistula (an abnormal passageway between the heart and esophagus)
Fatigue	Extreme tiredness
Fever	Abnormally high body temperature
Headache	Pain in the head
Hemoptysis	Coughing up blood or blood-stained mucus
Hypotension/hypertension	Low/high blood pressure
Infection (e.g. sepsis)	Invasion and multiplication of microorganisms (e.g. bacteria, virus) not normally present within the body
Lightheadedness	Feeling faint, woozy, weak or unsteady
Myocardial infarction	Blockage of blood flow to the heart muscle (i.e. heart attack)
Nausea/vomiting	• Nausea: sensation of unease and discomfort in the upper stomach with an urge to vomit • Vomiting: forceful expulsion of stomach contents through the mouth and/or nose
Perforation	Unintended puncture through the wall of a blood vessel or cardiac tissue
Pericardial effusion	Fluid collecting in the sac that surrounds the heart
Pericarditis	Inflammation of the sac-like tissue that surrounds the heart

Adverse Event/Risk	Definition
Phrenic nerve injury	Damage to the nerve that controls breathing; may cause hiccups, involuntary spasm of the diaphragm and respiratory organs, or paralyze the diaphragm
Pleural effusion	Collection of extra fluid around the lungs
Pneumonia	Lung infection that inflames air sacs in one or both lungs
Pneumothorax	Collapsed lung
Pseudoaneurysm	Collection of blood in the tissue surrounding the catheter insertion site due to ongoing leaking of blood from a blood vessel
Pulmonary edema	Excess fluid in the lungs
Pulmonary vein stenosis	Blockage in the blood vessels takes blood from the lungs to the heart
Shortness of breath	Difficulty breathing
Shivering	Body shaking
Sore throat	Pain in throat
Transient ischemic attack	New focal neurological deficit with rapid symptom resolution (usually 1 to 2 hours), no more than 24 hours
Vagal nerve injury (e.g. gastroparesis)	Injury to the vagal nerve resulting in esophageal dysmotility or gastroparesis, including: • Delayed gastric emptying • Difficulty swallowing/narrowing of the esophagus • Digestive discomfort/pain in the abdomen
Valve damage with potential regurgitation	Damage to heart valve (e.g. tricuspid, mitral), including backward flow of blood through the valve
Vasovagal reaction	Reflex of the involuntary nervous system that causes the heart to slow down and blood pressure drops; may result in fainting
Visual changes	Changes to vision, including blurred vision and bilateral visual disturbance

Appendix D: Endpoint-Related Adverse Event Definitions

Table 15 describes definitions for a subset of endpoint-related adverse events that may be observed in the study.

Table 15: Adverse Event Definitions

Adverse Event	Definition
Atrioesophageal Fistula	Connection between the atrium and the lumen of the esophagus. Evidence supporting this diagnosis includes documentation of esophageal erosion combined with evidence of a fistulous connection to the atrium such as air emboli, an embolic event, or direct observation at the time of surgical repair.
Cardiac tamponade/ perforation	Development of a significant pericardial effusion during or within 30 days of undergoing the study ablation procedure. A significant pericardial effusion is one that results in hemodynamic compromise, requires elective or urgent pericardiocentesis, or results in a 1-cm or more pericardial effusion as documented by echocardiography.
Cerebrovascular accident/stroke	Rapid onset of a focal or global neurological deficit with at least one of the following: change in level of consciousness, hemiplegia, hemiparesis, numbness or sensory loss affecting one side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke. Confirmed by neurology assessment and/or radiographic confirmation.
Esophageal injury	Injury to the lumen of the esophagus that does not result in an atrioesophageal fistula. Confirmed by endoscopic examination.
Hemoptysis	Expectoration of blood or blood-tinged sputum from the lungs or tracheobronchial tree.
Lung Injury	Presence of any of the following: bronchial lesion, hemoptysis, constriction, pulmonary hemorrhage, bronchia fistula
Major bleeding	Bleeding that requires and/or is treated with transfusion or results in a 20% or greater fall in hematocrit.
Myocardial infarction	Presence of any one of the following criteria: 1) detection of ECG changes indicative of new ischemia (new ST-T changes or new LBBB), which persist for more than one hour; 2) development of new pathological Q waves on an ECG; 3) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
Pericarditis	Effusion that leads to hemodynamic compromise or requires pericardiocentesis, prolongs hospitalization by more than 48 hours, requires hospitalization, or persists for more than 30 days following the ablation procedure.

Adverse Event	Definition
Phrenic nerve injury	Absent phrenic nerve function as assessed by diaphragmatic fluoroscopy/sniff test that is ongoing from hospital discharge. Phrenic nerve injury is considered permanent when it is documented to be present 12 months or longer following ablation.
Pulmonary vein stenosis	Reduction of the diameter of a PV or PV branch. PV stenosis can be categorized as mild <50%, moderate 50%–70%, and severe ≥70% reduction in the diameter of the PV or PV branch.
Symptomatic persistent iatrogenic atrial septal defect	New atrial septal defect found by new on-set pulmonary hypertension (symptomatic) and assessed via ultrasound Doppler imaging.
Transient ischemic attack	New focal neurological deficit with rapid symptom resolution (usually 1 to 2 hours), no more than 24 hours. Confirmed by neurology assessment and/or radiographic confirmation.
Vagal nerve injury	Injury to the vagal nerve that results in esophageal dysmotility or gastroparesis (i.e. delayed gastric emptying).
Vascular access site complication	Development of a hematoma (excluding minor hematomas not requiring surgical treatment), AV fistula or pseudoaneurysm that requires intervention, prolongs the hospital stay, or requires hospital admission.

Appendix E: Draft Data Collection Elements (Case Report Forms)

Draft CRFs for the study will be provided under separate cover. Final CRFs will be provided to centers via the electronic data management system after the center has fulfilled all requirements for database access.

Appendix F: Informed Consent Template

The Informed Consent Template will be distributed under separate cover.

Appendix G: IRB/REB/MEC List

A final IRB/REB/MEC list has not been finalized prior to development of the Clinical Investigator Plan and will be distributed under separate cover.

Appendix H: Participating Investigators and Institutions

A final list of participating Investigators and institutions has not been finalized prior to development of the Clinical Investigation Plan and will be distributed under separate cover.

Appendix I: Pre-Clinical Testing

A summary of results from pre-clinical testing with the ArcticLine Catheter is provided in the Report of Prior Investigations Summary under separate cover.

17. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• Not Applicable, New Document	Mandi Rupp, Principal Clinical Research Specialist Jeff Cerkvenik, Senior Principal Statistician Kirsten Rasmussen, Clinical Research Specialist Craig Dull, Principal Field Clinical Engineer