| Medtronic<br>**Clinical Investigation Plan** | |
|---|---|
| **Clinical Investigation Plan/Study Title** | STOP Persistent AF |
| **Study Product Name** | Arctic Front Advance™ Cardiac CryoAblation Catheter<br>Freezor *MAX*® Cardiac CryoAblation Catheter |
| **Sponsor/Local Sponsor** | United States of America<br>Medtronic, Inc.<br>8200 Coral Sea Street NE<br>Mounds View, MN 55112<br>United States of America<br><br>Canada<br>Medtronic of Canada, Ltd.<br>99 Hereford Street<br>Brampton, Ontario, L6Y 0R3<br>Canada<br><br>Europe<br>Medtronic, Bakken Research Center B.V.<br>Endeplosdomein 5<br>6229 GW Maastricht<br>The Netherlands<br><br>Japan<br>Medtronic Japan Co. Ltd.<br>1-2-70 Konan<br>Minato-ku, Tokyo 108-0075<br>Japan |
| **Document Version** | 5, 17APR2017 |
| **Lead Co-Principal Investigator(s)/Coordinating Investigators** | Hugh Calkins, MD<br>Address: Johns Hopkins, 1800 Orleans Street, Zayed Tower 712R, Baltimore, MD 21287<br>Telephone: 410-955-7405<br>Fax: 410-614-1345<br>[redacted]<br>Professional Position: Nicholas J. Fortuin Professor of Cardiology, Division of Cardiology, The Johns Hopkins University School of Medicine. Professor of Medicine, Department of Medicine, Division of Cardiology, The Johns Hopkins University School of Medicine. Professor of Pediatrics, Department of Pediatrics, Division of Pediatric Cardiology, The Johns Hopkins University School of Medicine. Director of the Arrhythmia Service, |

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| | Clinical Electrophysiology Laboratory, and Arrhythmogenic Right Ventricular Dysplasia Program, The Johns Hopkins Hospital<br><br>Vivek Reddy, MD<br>Address: Mt. Sinai Heart, One Gustave L Levy Place, Box 1030, New York, NY 10029<br>Telephone: 212-241-7114<br>Fax: 646-537-9691<br>[redacted]<br>Professional Position: The Leona M. and Harry B. Helmsley Charitable Trust Professor of Medicine in Cardiac Electrophysiology |
| **Coordinating Investigator** | Wilbur Su, MD<br>Address: Banner-University Medical Group-Heart Center 1300 North 12th Street, Suite 407, Phoenix, AZ 58006<br>Telephone: 602-839-7393<br>[redacted]<br>Professional Position: Clinical Assoc. Professor of Medicine, University of Arizona, Chief of Cardiac EP, Banner-University Medical Center-Phoenix, Director of EP Fellowship, Banner-University Medical Center-Phoenix |



## 1. Version History

| Version | Summary of Changes | Rationale | Author(s)/Title |
|---|---|---|---|
| 1.0 | Not Applicable, New Document | Not Applicable, New Document | Dana Wigert, Sr. Prin. Clinical Research Specialist<br>Fred Kueffer, Pr. Statistician |
| 2.0 | Synopsis, Sections 7.1, 7.2 and 18: Modified the primary efficacy OPC and changed the atypical flutter treatment failure to any recurrence of atrial | FDA feedback | Dana Wigert, Sr. Prin. Clinical Research Specialist<br>Fred Kueffer, Pr. Statistician |

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| | flutter | | |
| 2.0 | Synopsis, Sections 7.1, 7.2 14.16 and 18.3.2: Changed the secondary safety objective to a primary safety objective with a pre-specified hypothesis | FDA feedback | Dana Wigert, Sr. Prin. Clinical Research Specialist<br>Fred Kueffer, Pr. Statistician |
| 2.0 | Synopsis, Sections 7.1, 7.2 and 18.5: Added an ancillary objective [redacted] | [redacted] | Dana Wigert, Sr. Prin. Clinical Research Specialist<br>Fred Kueffer, Pr. Statistician |
| 2.0 | Synopsis, Sections 7.1, 7.2 and 18.5: Added and ancillary objective [redacted] | [redacted] | Dana Wigert, Sr. Prin. Clinical Research Specialist<br>Fred Kueffer, Pr. Statistician |
| 2.0 | Synopsis, Sections 7.1, 7.2 and 18.5: Removed [redacted] ancillary objective | [redacted] | Dana Wigert, Sr. Prin. Clinical Research Specialist<br>Fred Kueffer, Pr. Statistician |
| 2.0 | Synopsis, Sections 5, 8 and 18: Study data from the Japanese centers will not be included in the PMA-S submission, but will be included in a submission to Japan Pharmaceuticals and Medical Device Agency (PMDA) | Participation and enrollment in Japan is anticipated to start later than the other geographies | Dana Wigert, Sr. Prin. Clinical Research Specialist<br>Fred Kueffer, Pr. Statistician |
| 2.0 | Table 5: Noted the complication definition may vary from study to study | Clarification | Dana Wigert, Sr. Prin. Clinical Research Specialist<br>Fred Kueffer, Pr. Statistician |
| 2.0 | Sections 14 and 20.2: Added weekly and symptom driven event monitoring | FDA feedback and consistent with the 2012 HRS Expert Consensus Statement on Catheter and Surgical Ablation of AF | Dana Wigert, Sr. Prin. Clinical Research Specialist<br>Fred Kueffer, Pr. Statistician |

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| 2.0 | Sections 7.2.1, 14.7 and 18.3: Modified the antiarrhythmic dose allowed after the blanking period to historic maximum | FDA feedback | Dana Wigert, Sr. Prin. Clinical Research Specialist<br>Fred Kueffer, Pr. Statistician |
| 2.0 | Sections 7.2.1 and 18: 12-lead ECGs need to demonstrate at least 10 seconds of an atrial arrhythmia to be considered a treatment failure | Aligns with standard practice and FDA feedback | Dana Wigert, Sr. Prin. Clinical Research Specialist<br>Fred Kueffer, Pr. Statistician |
| 2.0 | Section 8.2: Rationale was updated | Consistent with the addition of a primary safety objective | Dana Wigert, Sr. Prin. Clinical Research Specialist<br>Fred Kueffer, Pr. Statistician |
| 2.0 | Section 14.1: Added review of symptoms suggestive of recurrent AF/AT/AFL to the study procedures and data collection table | Clarification | Dana Wigert, Sr. Prin. Clinical Research Specialist<br>Fred Kueffer, Pr. Statistician |
| 2.0 | Section 14.4: Added When performed, the TEE should be occur within 1 day (on the day of or within the day prior to) the planned ablation procedure | Clarification | Dana Wigert, Sr. Prin. Clinical Research Specialist<br>Fred Kueffer, Pr. Statistician |
| 2.0 | Section 14.5.5: Require CTI ablation if typical flutter has been documented or was induced. Recommend induction if not in the documented history. | FDA feedback | Dana Wigert, Sr. Prin. Clinical Research Specialist<br>Fred Kueffer, Pr. Statistician |
| 2.0 | Sections 7.2.1, 7.2.3, 14.5.5, 14.8, 18.3, and 18.5: removed the limitation that only CTI ablations are allowed in the right atrium | Allows for treatment of pre-existing right atrial arrhythmias that may contribute to the primary objective if left untreated | Dana Wigert, Sr. Prin. Clinical Research Specialist<br>Fred Kueffer, Pr. Statistician |
| 2.0 | Section 14.18: Added that | Compliance percentage will be | Dana Wigert, Sr. Prin. Clinical |

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| | a study deviation is not required if a subject misses a weekly TTM transmission. | managed by the core lab | Research Specialist<br>Fred Kueffer, Pr. Statistician |
| 2.0 | Section 17: Added that associated imaging studies may be requested, if available, for all serious adverse events with possible relatedness to the system or procedure | To support adverse event adjudication | Dana Wigert, Sr. Prin. Clinical Research Specialist<br>Fred Kueffer, Pr. Statistician |
| 2.0 | Section 18: Provided details regarding the determination of subjects for data analysis | FDA feedback | Dana Wigert, Sr. Prin. Clinical Research Specialist<br>Fred Kueffer, Pr. Statistician |
| 2.0 | Section 18.4: Provided details on the Hommel stepwise procedure for the secondary objectives | FDA feedback | Dana Wigert, Sr. Prin. Clinical Research Specialist<br>Fred Kueffer, Pr. Statistician |
| 2.0 | Section 18.5: Stated that ancillary objectives been defined to provide additional information about the performance of the Arctic Front Advance Cardiac CryoAblation Catheter. No hypotheses are defined for regulatory or labeling purposes. | FDA feedback | Dana Wigert, Sr. Prin. Clinical Research Specialist<br>Fred Kueffer, Pr. Statistician |
| 2.0 | Section 21.3: Removed Ltd reference. | Typo | Dana Wigert, Sr. Prin. Clinical Research Specialist<br>Fred Kueffer, Pr. Statistician |
| 3.0 | Section 18.3.2: Revised primary safety hypothesis statement and endpoint definition | Typo | Dana Wigert, Sr. Prin. Clinical Research Specialist<br>Fred Kueffer, Pr. Statistician |
| 4.0 | Sections 5, 8 and 18.2: Included additional details about the sample size in relation to Japanese data and how Japanese data will be reported | FDA feedback | Dana Wigert, Sr. Prin. Clinical Research Specialist<br>Fred Kueffer, Pr. Statistician |

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| 5.0 | Page 2: Removed Dr. Robert Kowal from the list of Coordinating Investigators | Dr. Robert Kowal no longer functions as a practicing physician | Dana Wigert, Sr. Prin. Clinical Research Specialist<br>Fred Kueffer, Sr. Prin. Statistician |
| 5.0 | Section 3: Updated Japan Monitoring contact | New information | Dana Wigert, Sr. Prin. Clinical Research Specialist<br>Fred Kueffer, Sr. Prin. Statistician |
| 5.0 | Table 4 and 6: Removed model number 990063-020 | Typo | Dana Wigert, Sr. Prin. Clinical Research Specialist<br>Fred Kueffer, Sr. Prin. Statistician |
| 5.0 | Sections 5 and 12.4: Increased the BMI cut off to 40 | Insufficient patient population to support enrollment requirement | Dana Wigert, Sr. Prin. Clinical Research Specialist<br>Fred Kueffer, Sr. Prin. Statistician |
| 5.0 | Section 9.1.4: Added the Achieve Advance Mapping Catheter | Device is now commercially available | Dana Wigert, Sr. Prin. Clinical Research Specialist<br>Fred Kueffer, Sr. Prin. Statistician |
| 5.0 | Sections 9.2 and 9.3: The Manual Retraction Kits will be investigational in Japan and tracked accordingly | PMDA feedback | Dana Wigert, Sr. Prin. Clinical Research Specialist<br>Fred Kueffer, Sr. Prin. Statistician |
| 5.0 | Section 14.19: Removed Subject has completed follow up as an exit choice | Completed follow up will be documented by completion of the 12 month office visit requirements | Dana Wigert, Sr. Prin. Clinical Research Specialist<br>Fred Kueffer, Sr. Prin. Statistician |
| 5.0 | Section 15.1: Changed pelvic to phrenic | Typo | Dana Wigert, Sr. Prin. Clinical Research Specialist<br>Fred Kueffer, Sr. Prin. Statistician |
| 5.0 | Table 11: Changed Article 273 to 274.2 for Japan Regulatory Authorities Sponsor responsibility reporting of SAEs and | Typo | Dana Wigert, Sr. Prin. Clinical Research Specialist<br>Fred Kueffer, Sr. Prin. Statistician |

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|---|---|---|---|
| | UADEs/USADEs | | |

## Table of Contents

# 2. Glossary

**Table 1: Glossary**

| Term | Definition |
|---|---|
| AE | Adverse event |
| AF | Atrial fibrillation |
| AAD | Antiarrhythmic drug |
| ACC | American College of Cardiology |
| ACT | Activated clotting time |
| ADE | Adverse device effect |
| AFL | Atrial flutter |
| AHA | America Heart Association |
| AT | Atrial tachycardia |
| AFEQT | Atrial fibrillation effect on quality-of-life questionnaire |
| BMI | Body mass index |
| C | Celsius |
| CT | Computed tomography |
| CV | Curriculum vitae |
| CEC | Clinical Events Committee |
| CFE | Complex fractionated electrograms |
| CFR | Code of Federal Regulations |
| CIP | Clinical investigation plan |
| CRF | Case report form |
| CTA | Clinical trial agreement |
| DC | Direct current |

| | |
|---|---|
| DD | Device deficiency |
| e.g. | For example |
| ECG | Electrocardiogram |
| ECAS | European Cardiac Arrhythmia Society |
| ECRF | Electronic case report form |
| EHRA | European Heart Rhythm Association |
| F | Fahrenheit |
| FD | Financial disclosure |
| FAL | Foreseeable adverse event list |
| FDA | Food and Drug Administration |
| FDAAA | Food and Drug Administration Amendments Act |
| GCP | Good clinical practice |
| GEE | Generalized estimating equation |
| HR | Hazard ration |
| HRS | Heart Rhythm Society |
| HOMI | Head of medical institution |
| ID | Identification |
| IDE | Investigational device exemption |
| Inc | Incorporated |
| IRB | Institutional review board |
| ISO | International Organization for Standardization |
| ICMJE | International Committee of Medical Journal Editors |
| LAD | Left atrial diameter |
| LVEF | Left ventricular ejection fraction |
| MDD | Medical device directive |

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|---|---|
| MEC | Medical ethics committee |
| MHLW | Ministry of Health, Labour and Welfare |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NOAC | Novel oral anticoagulant |
| NYHA | New York Heart Association |
| N2O | Nitrous Oxide |
| OPC | Objective performance criteria |
| PV | Pulmonary vein |
| PAF | Paroxysmal atrial fibrillation |
| PCI | Percutaneous coronary intervention |
| PIC | Patient informed consent |
| PVI | Pulmonary vein isolation |
| PTCA | Percutaneous transluminal coronary angioplasty |
| PMDA | Pharmaceuticals and Medical Devices Agency |
| PMA-S | Premarket Approval Supplement |
| RF | Radiofrequency |
| RI | Right inferior |
| RS | Right superior |
| SD | Standard deviation |
| SF | Short form |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SCD | Sudden cardiac death |
| SADE | Serious adverse device effect |
| TEE | Transesophageal echocardiogram |

| | |
|---|---|
| TIA | Transient ischemic attack |
| TTE | Transthoracic echocardiogram |
| TTM | Trans-telephonic monitoring |
| US | United States |
| UADE | Unanticipated adverse device effect |
| USADE | Unanticipated serious adverse device effect |

## 3. Sponsor Contacts

Regional contact information is provided below. This information may be subject to change during the course of the study. Periodic updates to study contact information will be sent to centers as needed.

**Table 2: Study Sponsor Contact Information**

| | |
|---|---|
| **Study Contacts** | Worldwide and US Clinical Study Leader<br>Dana Wigert, Principal Clinical Research Specialist<br>Direct Phone: 763-526-2802<br>[redacted]<br>Direct Fax: 763-367-1727<br>Email: dana.wigert@medtronic.com<br><br>*Europe*<br>Daniel Becker, Senior Clinical Research Specialist<br>Direct Phone: 49 215981490<br>Direct Fax: 49 21598149100<br>Email: daniel.becker@medtronic.com<br><br>*Canada*<br>Mary McCann, Senior Clinical Research Specialist<br>Direct Phone: 905-460-3639<br>Direct Fax: 905-460-3998<br>Email: mary.mccann@medtronic.com<br><br>*Japan*<br>Yoshiko Ishiwatari, Senior Clinical Research Specialist<br>Direct Phone: 81-3 6776-0105<br>Direct Fax: 81-3 6774-4705<br>Email: yoshiko.ishiwatari@medtronic.com |
| **Monitoring Contacts** | *US, Canada*<br>Beth Ornell, Clinical Monitoring Manager<br>Direct Phone: 508-261-8000<br>Email: beth.a.ornell@medtronic.com |

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| | *Europe*<br>Anja Hesse, Clinical Monitoring Manager<br>Direct Phone: 49215981490<br>Direct Fax: 4921027069069<br>Email: anja.hesse@medtronic.com<br><br>Japan<br>Hitomi Yoshida, Senior Clinical Research Specialist<br>Direct Phone: 81-3 6776-0775<br>Direct Fax: 81-3 6774-4705<br>Email: hitomi.yoshida@medtronic.com |

## 4. CROs/Core Laboratories

This information may be subject to change during the course of the clinical study. Periodic updates to contact information will be sent to centers as needed.

**Table 3: CRO and Core Laboratory Information**

| Contact Information | Duties performed |
|---|---|
| *Cognizant Technology Solutions*<br>500 Frank W. Burr Blvd.<br>Teaneck, NJ 07666<br>Direct Phone: (201) 801-0233<br>Direct Fax: (201) 801-0243 | • Development of study electronic case report forms, edit checks, and study management reports.<br>• Review of electronic case report forms, management of discrepancies, and coding of medications and deviations. |
| *Holter, trans-telephonic monitors (TTM) and 12-lead ECG Core Laboratory*<br>Contact provided under separate cover | • Distribution of Holters, TTMs and 12-lead ECG machines<br>• Adjudication of atrial arrhythmias |

## 5. Synopsis

**Table 4: Study Synopsis**

| | |
|---|---|
| **Title** | STOP Persistent AF study |
| **Clinical Study Type** | Pivotal |
| **Product Name** | Arctic Front Advance™ Cardiac CryoAblation Catheter<br>Freezor *MAX*® Cardiac CryoAblation Catheter |

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|---|---|
| **Sponsor** | *United States of America*<br>Medtronic, Inc.<br>8200 Coral Sea Street NE<br>Mounds View, MN 55112<br>United States of America |
| **Local Sponsor** | *Canada*<br>Medtronic of Canada, Ltd.<br>99 Hereford Street<br>Brampton, Ontario, L6Y 0R3<br>Canada<br><br>*Europe*<br>Medtronic, Bakken Research Center B.V.<br>Endeplosdomein 5<br>6229 GW Maastricht<br>The Netherlands<br><br>*Japan*<br>Medtronic Japan Co. Ltd.<br>1-2-70 Konan<br>Minato-ku, Tokyo 108-0075<br>Japan |
| **Indication under investigation** | The proposed indication for the Arctic Front Advance CryoAblation Catheter is as follows: The Arctic Front Advance Cardiac CryoAblation Catheters are indicated for the treatment of drug refractory recurrent symptomatic paroxysmal and persistent atrial fibrillation.<br><br>The proposed indication for the Freezor *MAX* Cardiac CryoAblation Catheter is as follows: The Freezor *MAX* Cardiac CryoAblation Catheters are indicated for use as an adjunctive device in the endocardial treatment of paroxysmal and persistent 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.<br><br>These proposed indications are outside of the approved indications in the United States and Japan but are within the approved indications in Europe and Canada. |
| **Investigation Purpose** | To demonstrate safety and effectiveness of the Arctic Front Advance and Freezor MAX Cardiac CryoAblation Catheters for the treatment of drug refractory recurrent symptomatic persistent atrial fibrillation (AF). |

<table>
<tr><td>Product Status</td><td>
<table>
<tr><th>Component</th><th>Model Number</th><th>Geography</th><th>Manufacturer</th></tr>
<tr><td rowspan="4">Arctic Front Advance Cardiac CryoAblation Catheter</td><td>2AF234</td><td rowspan="2">US (investigational)<br>Japan (investigational)</td><td rowspan="2">Medtronic, Inc.</td></tr>
<tr><td>2AF284</td></tr>
<tr><td>2AF233</td><td rowspan="2">Canada (non-investigational)<br>Europe (non-investigational)</td><td rowspan="2">Medtronic, Inc.</td></tr>
<tr><td>2AF283</td></tr>
<tr><td rowspan="4">Freezor MAX Cardiac CryoAblation Catheter</td><td>239F3</td><td rowspan="2">US (investigational)<br>Japan (investigational)</td><td rowspan="2">Medtronic, Inc.</td></tr>
<tr><td>239F5</td></tr>
<tr><td>209F3</td><td rowspan="2">Canada (non-investigational)<br>Europe (non-investigational)</td><td rowspan="2">Medtronic, Inc.</td></tr>
<tr><td>209F5</td></tr>
</table>
</td></tr>
<tr><td>Primary Objectives</td><td>1. Demonstrate an acceptable efficacy success rate at 12 months after the pulmonary vein isolation (PVI) ablation procedure.<br>2. Demonstrate an acceptable safety profile of the pulmonary vein isolation (PVI) ablation procedure.</td></tr>
<tr><td>Secondary Objective</td><td>1. Demonstrate an improvement in quality of life between baseline and 12 months as measured by the Atrial Fibrillation Effect on QualiTy-of-life Questionnaire (AFEQT) and Medical Outcome Study Short Form-12 (SF-12) questionnaires</td></tr>
<tr><td>Ancillary Objectives</td><td>[redacted]</td></tr>
<tr><td>Study Design</td><td>The study is prospective, interventional, multi-center, non-randomized, single arm, unblinded clinical study. The study will be conducted at up to 25 centers located in the US, Canada, Europe and Japan. The study objectives will be analyzed for a Premarket Approval Supplement (PMA-S) after all subjects from the US, Canada and Europe complete 12 months of follow-up after the index ablation procedure.<br><br>Study data from the Japanese centers will not be included in the PMA-S submission, but will be included in a submission to Japan Pharmaceuticals and Medical Device Agency (PMDA).</td></tr>
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| | The Japanese subjects are required by PMDA to support an expanded indication to the persistent AF population in Japan. The PMDA cohort will be analyzed separate to the PMA-S because participation and enrollment in Japan is anticipated to start later than the rest of the PMA-S cohort. |
| **Sample Size and Analysis Timing** | Up to 225 subjects will be enrolled world-wide. In the US, Canada and Europe, up to 200 subjects will be enrolled to ensure 150 subjects are treated with an Arctic Front Advance Cardiac CryoAblation Catheter. The maximum number of subjects treated at Canadian and European centers combined is 45 subjects.<br><br>Up to 25 subjects will be enrolled in Japan to ensure15 subjects are treated with an Arctic Front Advance Cardiac CryoAblation Catheter.<br><br>At the completion the last 12 month visit from the 150 enrolled and treated subjects from the US, Canada and Europe, a PMA-S will be submitted to the FDA. Study data from the Japanese centers will not be included in the PMA-S submission but will be made available.<br><br>A final report will be submitted to Japan PMDA at the completion of the last 12 month visit from the 15 treated Japanese subjects. Study data from all 165 treated subjects will be included in this report. |
| **Inclusion/Exclusion Criteria** | **Inclusion Criteria**<br>• Documentation of symptomatic persistent AF<br>  ○ Defined as having a continuous episode lasting longer than 7 days but less than 6 months documented by consecutive ECG recordings<br>• Failure or intolerance of at least one Class I or III antiarrhythmic drug<br>• Age 18 (or older if required by local law) to 80<br><br>**Exclusion Criteria**<br>• Left atrial diameter > 5.0 cm (anteroposterior)<br>• Prior left atrial ablation or surgical procedure (including left atrial appendage closures)<br>• Presence or likely implant of a permanent pacemaker, biventricular pacemaker, loop recorder, or any type of implantable cardiac defibrillator (with or without biventricular pacing function) within 12 months<br>• Body mass index (BMI) >40<br>• Presence of any pulmonary vein stents<br>• Presence of any pre-existing pulmonary vein stenosis<br>• Pre-existing hemidiaphragmatic paralysis<br>• Presence of any cardiac valve prosthesis<br>• Moderate or severe mitral valve regurgitation or stenosis<br>• Any cardiac surgery, myocardial infarction, PCI / PTCA or coronary artery stenting which occurred during the 3 month interval preceding the consent date<br>• Unstable angina<br>• NYHA Class IV congestive heart failure and/or documented left ventricular ejection fraction (LVEF) less than 45% measure by acceptable cardiac testing (e.g. TTE)<br>• Primary pulmonary hypertension |

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|---|---|
| | • Rheumatic heart disease<br>• Thrombocytosis, thrombocytopenia<br>• Any condition contraindicating chronic anticoagulation<br>• Active systemic infection<br>• Hypertrophic cardiomyopathy<br>• Cryoglobulinemia<br>• Uncontrolled hyperthyroidism<br>• Any cerebral ischemic event (strokes or TIAs) which occurred during the 6 month interval preceding the consent date<br>• Any woman known to be pregnant or breastfeeding, or any woman of child bearing potential who is not on a reliable form of birth regulation method or abstinence<br>• Life expectancy less than one year<br>• Current or anticipated participation in any other clinical trial of a drug, device or biologic during the duration of the study not pre-approved by Medtronic<br>• Known allergies or hypersensitivities to adhesives<br>• Known drug or alcohol dependency<br>• Unwilling or unable to comply fully with study procedures and follow-up |
| **Study Procedures and Assessments** | Subjects are assessed for eligibility at a baseline visits and then undergo a cryoablation procedure followed by hospital discharge. All subjects are contacted by phone 6 weeks after the ablation procedure, are seen in the office at 3, 6 and 12 months after the index ablation procedure, and are then exited from the study. |

# 6. Introduction

## 6.1. Background

Atrial fibrillation 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. AF can be clinically stratified based on whether episodes are self-terminating (paroxysmal) or persistent. Paroxysmal AF (PAF) is defined as recurrent AF (≥2 episodes) that terminates spontaneously within 7 days. Persistent AF is defined as continuous AF that is sustained for greater than 7 days.[1]

[1] Calkins, H., et al., HRS/EHRA/ECAS expert Consensus Statement on catheter and surgical ablation of atrial fibrillation: recommendations for Patient selection, procedural techniques and follow-up, definitions, endpoints and research trial design. A report of the Heart Rhythm Society (HRS) Task Force on catheter and surgical ablation of atrial fibrillation. Heart Rhythm. 2012; 9(4): p. 632-696.e20.

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[2], and that number is expected to double over the next 25 years.[3] 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 persistent AF. Persistent AF represents approximately 25% of AF cases.[4] 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.[5] In comparison to patients with PAF, patients with persistent AF are at a 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).[6]

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".[2] 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 2012, the HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation published a Class IIa Level B recommendation 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".[1] In the 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]

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).[7, 8] AF arises primarily from the left side of the heart in (or near) the atrium, particularly where the pulmonary veins (PVs)

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[2] January C, Wann L, Alpert J, Calkins H, 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.

[3] Go A, Hylek E, Phillips K, 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.

[4] Zoni-Berisso M, Lercari F, Carazza T, Domenicucci S. Epidemiology of atrial fibrillation: European perspective. Clinical Epidemiology. 2014;6:213-220. doi:10.2147/CLEP.S47385.

[5] Wolf P, Abbott R, Kannel W. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke. 1991;22(8):983-988.

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

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

[8] Jais P, O'Neill MD, Takahashi Y, 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.

join the atrium. The fundamental basis for the AF ablation procedure is the creation of myocardial lesions that block the propagation of AF wave fronts from the triggering source. The muscular sleeves within the PVs have been established as a critical source of AF triggers.[9]

Historically, the stepwise approach was introduced over 10 years ago as the ablation strategy for patients with persistent AF.[8,10] 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 entire stepwise strategy has been the topic of reevaluation as outcomes may have been more biased by patient cohorts rather than ablation strategy.[11]

Three recent studies call into question the stepwise ablation approach as each study reporting benefit using a minimal PVI-only type strategy.[12,13,14,15] In the 2C3L study, an extensive ablation group which included complex fractionated electrograms (CFE) ablation had a trend towards worse outcomes compared to a control cohort with less extensive ablation.[12] Similarly, in the Wynn et al. 2015 study, PVI alone had a trend towards better outcomes compared to PVI ablation with the addition of linear line ablation. Finally, the pivotal STAR AF II results demonstrated the benefits of a PVI-only approach over that of additional linear ablation or CFE ablation. This trial compared the efficacy of three different AF ablation strategies in 589 patients with persistent AF. Subjects were randomized to PVI alone, PVI plus complex fractionated electrograms (PVI+CFE), and PVI plus linear ablation (PVI+Lines). The STAR AF II trial outcomes were:

- Additional CFE or Lines ablation increased procedural time
- No benefit in AF reduction when additional substrate ablation (CFE or Lines) was performed in addition to PVI.
- PVI alone achieved freedom from recurrence in 59% of patients at 18 months

The stepwise ablation studies may have suffered from the inability to create a robust and durable PVI as a foundational strategy (with historic focal RF ablation catheters), which could have adversely changed the data interpretation of the results. More recent studies have examined and compared the ability of cryoballoon technology to create a robust and durable PVI compared to RF catheters. Aryana et al. in a large,

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[9] 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.
[10] Rostock T, Steven D, Hoffman B, 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.
[11] 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
[12] Dong JZ, Sang CH, Yu RH, et al. Prospective randomized comparison between a fixed "2C3L" approach vs. stepwise approach for catheter ablation of persistent atrial fibrillation. *Europace*. doi:10.1093/europace/euv067.
[13] Wynn GJ, Panikker S, Morgan M, et al. Effect of linear ablation in substrate-based AF: Results of the substrate modification with ablation and antiarrhythmic drugs in non-permanent atrial fibrillation trial. *Heart Rhythm*. 2015;12:1715.
[14] Verma A, Jiang CY, Betts TR, et al, STAR AF II Investigators. Approaches to Catheter Ablation for Persistent Atrial Fibrillation. *N Engl J Med*. 2015;372:1812-1822.
[15] Scott P, Silberbauer J, Murgatroyd F. The impact of adjunctive complex fractionated atrial electrograms ablation and linear lesions on outcomes in persistent atrial fibrillation: a meta-analysis. *Europace 2016; 18, 359-367.*

multicenter study demonstrated the superiority of the Arctic Front Advance catheter at creating durable PVI and better long-term outcomes as a result of the robust PVI (freedom from AF/AT/AFL at 12 months following a single procedure without AADs was 76.6% vs 60.4%, p<0.001 and less repeat ablations, 14.6% vs 24.1%, p<0.001).[16] Consequently, PVI remains an important foundational ablation strategy for the treatment of both paroxysmal and persistent AF, and previous ablations strategies, including stepwise, may have been hampered by the inability to create long-term PVI.

The safety profile of cryoballoon ablation is also well established. The STOP AF trial[17] was a prospective, multicenter, randomized, controlled investigation device exemption (IDE) study designed to compare outcomes of cryoballoon and antiarrhythmic drug therapies in patients with PAF. The cryoballoon arm met its primary safety objective with a serious procedure related event rate of 3.1%. Comparing safety rates versus the AAD arm, 6.1% of cryoballoon subjects experienced a serious procedure-related event or major adverse event versus 8.5% of AAD subjects. An analysis of 149 cryoballoon studies with 11,242 patients (see Appendix A for literature search methodology) showed similar complication rates to STOP AF for both PAF and persistent AF patients (see Table 5).

**Table 5: Safety Summary of Cryoballoon Literature**

| Atrial Fibrillation Type (Number patients, studies) | Complications %* |
|---|---|
| Paroxysmal AF (n = 5736; 82 studies) | 6.12% |
| Persistent AF (n= 843; 17 studies) | 4.63% |
| Paroxysmal/persistent AF combined (n= 4663; 56 studies) | 6.26% |
| All Atrial Fibrillation (n=11,242; 149 studies) | 6.07% |

*The complication definition may vary from study to study.

Expanded indications in the US would fulfill an unmet clinical need for symptomatic persistent AF patients in which antiarrhythmic drugs fail or are not tolerated.

## 6.2. Purpose

The purpose of the study is to provide data demonstrating the safety and effectiveness of the Arctic Front Advance and Freezor MAX Cardiac CryoAblation Catheters for the treatment of symptomatic drug refractory persistent AF. The study is proposed by the sponsor as a result of feedback received from the US Food and Drug Administration (FDA) on pre-submission Q151184, regarding a proposal to expand the

[16] Aryana A, Singh SM, Kowalski M, et al. Acute and Long-Term Outcomes of Catheter Ablation of Atrial Fibrillation Using the Second-Generation Cryoballoon versus Open-Irrigated Radiofrequency: A Multicenter Experience. *J Cardiovasc Electrophysiol*. 2015 Aug;26(8): 832-9.
[17] Packer D, Kowal R, Wheelan K, Irwin J, Champagne J, Guerra P, Dubuc M, Reddy V, Nelson L, Holcomb R, Lehmann J, Ruskin J. *J Am Coll Cardiol*. 23 April 2013. 61(16):1713-1723.

indications for use for the Arctic Front Advance to include patients with persistent AF. The study is also designed to expand the indication for the Freezor *MAX* Cardiac CryoAblation Catheter. The proposed indication for the Arctic Front Advance CryoAblation Catheter is as follows: The Arctic Front Advance Cardiac CryoAblation Catheters are indicated for the treatment of drug refractory recurrent symptomatic paroxysmal and persistent atrial fibrillation. The proposed indication for the Freezor *MAX* Cardiac CryoAblation Catheter is as follows: The Freezor *MAX* Cardiac CryoAblation Catheters are indicated for use as an adjunctive device in the endocardial treatment of paroxysmal and persistent 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.

[redacted]

# 7. Objectives and Endpoints

## 7.1. Objectives

### 7.1.1. Primary Objectives

#### 7.1.1.1. Primary Efficacy Objective

Demonstrate an acceptable efficacy success rate at 12 months after the pulmonary vein isolation (PVI) ablation procedure.

#### 7.1.1.2. Primary Safety Objective

Demonstrate an acceptable safety profile of the pulmonary vein isolation (PVI) ablation procedure.

### 7.1.2. Secondary Objective

Demonstrate an improvement in quality of life between baseline and 12 months after the index ablation procedure as measured by the AFEQT and SF-12 questionnaires.

### 7.1.3. Ancillary Objectives

[redacted]

[redacted]

## 7.2. Endpoints

### 7.2.1. Primary Endpoints

1. Primary Efficacy: Demonstrate an acceptable efficacy success rate at 12 months after the pulmonary vein isolation (PVI) ablation procedure.

   Treatment success is defined as freedom from treatment failure. Treatment failure is defined as any of the following components:
   - Acute procedural failure
   - Documented AF/AT/AFL on Holter/TTM/12-lead ECG after the 90 day blanking period
     - Minimum of 30 seconds on Holter/TTM and 10 seconds on 12-lead ECG
   - A reablation for the treatment of recurrent AF/AT/AFL after the 90 day blanking period
   - Class I or III antiarrhythmic drug (AAD) dose increase from the historic maximum ineffective dose (prior to the ablation procedure) or initiation of a new Class I or III AAD after the 90 day blanking period. Note: remaining on the same pre-ablation dose or decreased dose, or re-initiation of a previously failed or not tolerated Class I or III AAD after the 90 day blanking is not considered a failure.
   - Ablation using RF in the left atrium

Blanking period is defined as the first 90 days after the index ablation procedure. Recurrences of atrial arrhythmias during the blanking period will not be counted in the determination of the first clinical failure for the primary endpoint. Within the blanking period, recurrent arrhythmias can be managed with antiarrhythmic drugs, cardioversion or one cryo re-ablation procedure of the pulmonary veins. Titration of Class I and III antiarrhythmic medications are allowed during the blanking period. Subjects are allowed to remain on Class I or III antiarrhythmic medications at the historic maximum ineffective dose (on prior to the ablation procedure) after the 90 day post-procedure blanking period.

Acute procedural failure is defined as:
- Inability to isolate all accessible targeted pulmonary veins (minimally assessed for entrance block and, where assessable, exit block) during the index procedure
- Left atrial non-PVI ablations including but not limited to, ablation of linear lesions complex fractionated electrograms or non-PV triggers

2. Primary Safety: Demonstrate an acceptable safety profile of the pulmonary vein isolation (PVI) ablation procedure.

   A primary safety event is defined as a serious procedure-related or serious system-related adverse event including the following:
   - Transient ischemic attack (within 7 days of ablation procedure)
   - Cerebrovascular accident (within 7 days of ablation procedure)
   - Major bleeding that requires transfusion (within 7 days of ablation procedure)

- Cardiac perforation, tamponade or pericardial effusion (within 7 days of ablation procedure)
- Pulmonary vein stenosis (> 75% reduction within 12-months of ablation procedure)
- Myocardial infarction (within 7 days of ablation procedure)
- Phrenic nerve injury (unresolved at 12-months)
- Atrio-esophageal fistula (within 12-months of ablation procedure)
- Death (within 7 days of ablation procedure)

### 7.2.2. Secondary Endpoint

Demonstrate an improvement in quality of life between baseline and 12 months after the index ablation procedure as measured by the AFEQT and SF-12 questionnaires.

- The (AFEQT) and (SF-12) questionnaires will be utilized for this objective. The AFEQT questionnaire is an atrial fibrillation specific health-related quality of life questionnaire to assess the impact of AF on a subject's life. The overall score ranges from 0 – 100, where 0 corresponds to complete disability and 100 corresponds to no disability. The SF-12 questionnaire is a quality of life questionnaire that evaluates the subject's mental and physical performance. Physical and mental health composite scores are calculated using responses to 12 questions with a response range from 0 to 100, where a 0 score indicates the lowest level of health measured by the scale and 100 indicates the highest level of health.

### 7.2.3. Ancillary Endpoints

[redacted]

## 8. Study Design

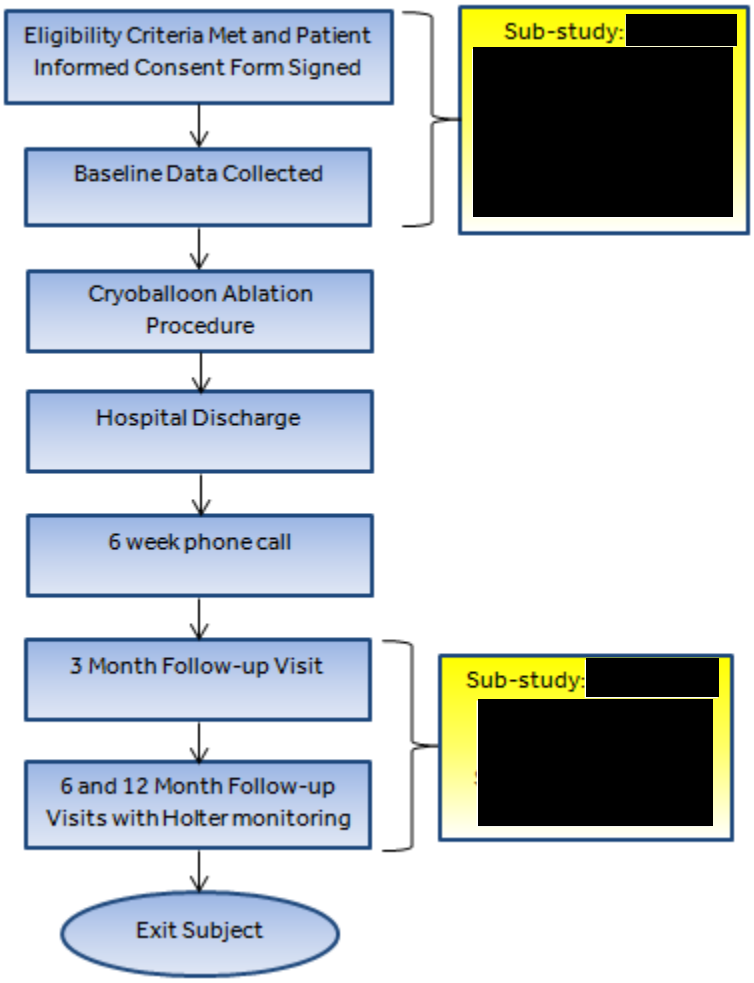
Medtronic, Inc. is sponsoring the STOP Persistent AF Study; a prospective, interventional, multi-center, non-randomized, single arm, unblinded clinical study. The study design diagram is shown in Figure 1.

Up to 225 subjects will be enrolled world-wide. In the US, Canada and Europe, up to 200 subjects will be enrolled to ensure 150 subjects are treated with an Arctic Front Advance Cardiac CryoAblation Catheter. The maximum number of subjects treated at Canadian and European centers combined is 45 subjects.

Up to 25 subjects will be enrolled in Japan to ensure15 subjects are treated with an Arctic Front Advance Cardiac CryoAblation Catheter. The maximum number of subjects treated at Japanese centers is 15 subjects.

It is anticipated that at least 165 Arctic Front Advance Cardiac CryoAblation Catheters will be used in this study. The maximum number of subjects that may be treated at a single center is 15 subjects (10% of the total treated in the PMA-S cohort).

**Figure 1: Study Design Flowchart**




## 8.1. Duration

Subjects from all geographies will be followed for 12 months after the index cryoballoon ablation procedure and then be exited from the study. Accordingly, the expected total study duration is approximately 2 years and 2 months, representing 14 months of enrollment and 12 months of subject follow-up. Subjects will not be replaced with newly enrolled subjects upon early study exit. The objectives will be analyzed for a Premarket Approval Supplement (PMA-S) after all subjects from the US, Canada and Europe complete 12 months of follow-up after the index ablation procedure. Study data from the Japanese centers will not be included in the PMA-S submission. A final report will be submitted to Japan PMDA at the completion of the study.

### 8.2. Rationale

The study has primary objectives designed to evaluate the safety and effectiveness of the Arctic Front Advance and Freezor MAX Cardiac CryoAblation Catheters for treatment of drug refractory symptomatic persistent AF. In the United States, there are no ablation catheters approved to treat subjects with persistent AF. The study will provide subjects with more options for treatment and the possibility of improving their health, quality of life and a decrease in stroke risk. If successful, the STOP Persistent AF study will demonstrate meaningful therapeutic benefit in this underserved population. This evaluation will support an indication expansion for the treatment of recurrent, symptomatic persistent AF. The study will be considered successful if it meets the primary objectives, contingent upon FDA review and approval.

## 9. Product Description

### 9.1. General

In the US, Canada and Europe, centers will utilize the commercially released Arctic Front Advance Cardiac CryoAblation Catheters and Freezor *MAX* Cardiac CryoAblation Catheters (and future commercially released generations). In Japan, the devices will be provided to the centers. Instructions for use of the devices used in the study are provided in their respective manuals. Device information is provided in Table 6 and described below.

[redacted] Any changes made to these devices during the investigation will be subject to IDE Modification Reporting Requirements as applicable.

**Table 6: Device Information**

| Component | Model Number | Geography | Manufacturer |
|---|---|---|---|
| Arctic Front Advance CryoAblation Catheter | 2AF234 | US (investigational) | Medtronic, Inc. |
| | 2AF284 | Japan (investigational) | |
| | 2AF233 | Canada (non-investigational) | Medtronic, Inc. |
| | 2AF283 | Europe (non-investigational) | |
| Freezor *MAX* CryoAblation Catheter | 239F3 | US (investigational) | Medtronic, Inc. |
| | 239F5 | Japan (investigational) | |
| | 209F3 | Canada (non-investigational) | Medtronic, Inc. |
| | 209F5 | Europe (non-investigational) | |

### 9.1.1. Arctic Front Advance Cardiac CryoAblation Catheters

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

Investigational indication in the US and Japan: The Arctic Front Advance Cardiac CryoAblation Catheters are indicated for the treatment of drug refractory recurrent symptomatic paroxysmal and persistent atrial fibrillation.

Approved indication in Europe and Canada: The Arctic Front Advance Cardiac CryoAblation Catheter is indicated for the treatment of patients with atrial fibrillation.

The catheters are sterile, single use, minimally invasive intravascular balloon catheters specifically designed for tissue cryoablation. The Arctic Front Advance Cardiac CryoAblation Catheter is used together with the CryoConsole and related devices. Arctic Front Advance catheters are 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.

### 9.1.2. Freezor MAX Cardiac CryoAblation Catheters

Approved indication in the US and Japan: The Freezor *MAX* Cardiac CryoAblation Catheter is used as an adjunctive device in the endocardial treatment of paroxysmal atrial fibrillation in conjunction with the Arctic Front Advance Cardiac CryoAblation Catheter.

Investigational indication in the US and Japan: The Freezor *MAX* Cardiac CryoAblation Catheters are indicated for use as an adjunctive device in the endocardial treatment of paroxysmal and persistent 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.

Approved indication in Europe and Canada: The Freezor *MAX* Cardiac CryoAblation Catheter is intended for use in treatment of cardiac arrhythmias.

The Freezor *MAX* Cardiac CryoAblation Catheter is a flexible, steerable catheter used to ablate cardiac tissue. It is used together with the CryoConsole and related components. The 8mm tip of the focal Freezor *MAX* Cryocatheter 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.

### 9.1.3. FlexCath Advance Steerable Sheath

The FlexCath Advance Steerable Sheath is a percutaneous introducer fitted with a hemostasis valve to allow for introduction, withdrawal and swapping 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 FlexCath Advance Steerable Sheath is intended to allow sheath deflection to facilitate catheter positioning. It is supplied sterile and packaged together with a dilator.

### 9.1.4. Achieve and Achieve Advance Mapping Catheters

The Achieve and Achieve Advance Mapping Catheters are 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 and Achieve Advance Mapping Catheters are designed to obtain electrograms in the atrial regions of the heart.

### 9.1.5. CryoConsole

The console 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 system while the software provides the user interface subject information, procedure temperature, time set point in automatic mode and procedure data information.

### 9.1.6. Coaxial Umbilical

The sterile coaxial umbilical delivers the Nitrous Oxide (N2O) 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.

### 9.1.7. Electrical Umbilical

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

### 9.1.8. Manual Retraction Kit

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.

### 9.1.9. [redacted]

[redacted]

#### 9.1.10. Additional Study Devices

Medtronic may incorporate additional components, software, and devices into this clinical study as they receive appropriate license or regulatory approval and are released commercially by Medtronic in the region where they will be used providing that the scientific soundness of the study is not adversely affected as evaluated by Medtronic.

## 9.2. Packaging

In the US, Canada and Europe, the Arctic Front Advance and Freezor *MAX* CryoAblation Catheters and Manual Retraction Kits will not be labeled as investigational, as these devices will be considered investigational upon opening per the CIP. Commercially available products will be used for the study.

In Japan, the devices will be labeled "Exclusively for Clinical Research" and provided to the centers.

## 9.3. Product Receipt, Tracking and Storage

In the US, Canada and Europe, the study will utilize the market-released Arctic Front Advance and Freezor *MAX* Cardiac CryoAblation Catheters and Manual Retraction Kits with no study driven changes to the product or labeling. These devices will not be provided to the centers.

In Japan, the devices including the Manual Retraction Kits will be labeled "Exclusively for Clinical Research" and will be provided to the centers. These devices must be kept in a secure and locked location and only used for the study.

The Arctic Front Advance and Freezor *MAX* Cardiac CryoAblation Catheters will be considered investigational in the US and Japan when opened with the intent to use in the study; however non-investigational in Canada and Europe. The Manual Retraction Kits will be considered investigational only in Japan when opened with the intent to use in the study.

Arctic Front Advance and Freezor *MAX* distribution logs will be provided to the US and Japanese centers and will be used for tracking of all investigational product throughout the entire study. The logs must be maintained and updated when disposed of or returned to Medtronic. A Manual Retraction Kit distribution log will be provided only to Japanese centers and will be used for tracking this product throughout the entire study.

NOTE: this is a deviation to Section 18.1 of the ISO standard because device accountability for Arctic Front Advance and Freezor *MAX* Cardiac CryoAblation Catheters and Manual Retraction Kits will not be performed in Europe or Canada and only upon package opening in the US (full device accountability will take place in Japan starting with distribution from Medtronic).

In Japan, the Arctic Front Advance and Freezor *MAX* Cardiac CryoAblation Catheters and the Manual Retraction Kit must be stored in a secure location at the center. It is the responsibility of the Investigator to correctly handle, store, and track the investigational devices. These devices will be used only in the study according to the CIP. Investigational product disposition logs will be provided to the center and used for tracking the Arctic Front Advance and Freezor *MAX* Cardiac CryoAblation Catheters and the Manual Retraction Kits during the study. The logs must be maintained at each center and updated when the Arctic

Front Advance and Freezor *MAX* Cardiac CryoAblation Catheters and Manual Retraction Kits are received, opened, used/attempted, disposed of or returned to Medtronic.

## 10. Investigator/Investigational Center Selection

All clinical Investigators managing the subject's arrhythmia must be qualified practitioners and experienced in the diagnosis and treatment of subjects with atrial arrhythmias. Investigators performing the cryoablation procedure must have been trained in the handling of Arctic Front Advance Cardiac CryoAblation Catheters.

The role of the Principal Investigator is to implement and manage the day-to-day conduct of the clinical investigation as well as ensure data integrity and the rights, safety and well-being of the subjects involved in the clinical investigation.

The Principal Investigator and proposed investigational center shall:

- Be qualified by Medtronic AF Solutions training & education, and has gained relevant experience having performed at least 20 ablation procedures with Arctic Front Advance and associated products
- Have adequate time and resources to conduct the study throughout the duration of the study
- Have access to an adequate number of subjects in the persistent AF population to enroll 1-3 subjects per month
- Have the ability to comply with applicable IRB/MEC/HOMI and regulatory requirements
- Not be debarred, disqualified or working under sanctions in applicable regions
- Be willing to perform pulmonary vein isolation only for the treatment of persistent AF

Center personnel training will be completed prior to participation in this clinical study.

## 11. Center Activation

During the activation process (prior to subject enrollment), Medtronic will train center personnel on the CIP, relevant standards and regulations, informed consent, and on data collection and reporting tools. If new members join the study center team, they will receive training on the applicable clinical study requirements relevant to their role before contributing to the clinical study.

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

- IRB/MEC approval (and membership roster/voting list, as required by local law) of the current version of the CIP, Patient Informed Consent Form, subject facing materials, Report of Prior Investigation, Investigator Brochure as required by local laws and other materials, as necessary
- Regulatory authority approval or notification (as required per local law)
- Fully executed Clinical Trial Agreement (CTA) and Investigator Statement where applicable
- Financial Disclosure of Investigators
- Curriculum Vitae (CV) of Investigators and key members of the investigation center team (as required by local law) (in Europe, CVs are required for all center members who have been delegated tasks)
- Documentation of delegated tasks
- Documentation of study training

Documentation of delegated tasks must be completed prior to any person other than the Principal Investigator performing study activities.

Additional requirements imposed by the IRB/MEC and regulatory authority shall be followed.

In addition, all participating center staff must be trained on the current version of the CIP and must be delegated by the Principal Investigator to perform study related activities.

Medtronic will provide each study center with documentation of study center/Investigator readiness in the form of a center readiness letter; this letter must be received prior to subject enrollment. Additional center personnel included after the initial activation will be notified when all requirements have been completed.

# 12. Selection of Subjects

## 12.1. Study Population

The study population being studied is one that has documented persistent atrial fibrillation with generally good cardiovascular health.

## 12.2. Subject Enrollment

Patients will be screened to ensure they meet all of the inclusion and none of the exclusion criteria prior to study enrollment. IRB/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.

## 12.3. Inclusion Criteria

- Documentation of symptomatic persistent AF
  - Defined as having a continuous episode lasting longer than 7 days but less than 6 months documented by consecutive ECG recordings
- Failure or intolerance of at least one Class I or III antiarrhythmic drug
- Age 18 (or older if required by local law) to 80

### 12.4. Exclusion Criteria

- Left atrial diameter > 5.0 cm (anteroposterior)
- Prior left atrial ablation or surgical procedure (including left atrial appendage closures)
- Presence or likely implant of a permanent pacemaker, biventricular pacemaker, loop recorder, or any type of implantable cardiac defibrillator (with or without biventricular pacing function) within 12 months
- Body mass index (BMI) >40
- Presence of any pulmonary vein stents
- Presence of any pre-existing pulmonary vein stenosis
- Pre-existing hemidiaphragmatic paralysis
- Presence of any cardiac valve prosthesis
- Moderate or severe mitral valve regurgitation or stenosis
- Any cardiac surgery, myocardial infarction, PCI / PTCA or coronary artery stenting which occurred during the 3 month interval preceding the consent date
- Unstable angina
- NYHA Class IV congestive heart failure and/or documented left ventricular ejection fraction (LVEF) less than 45% measure by acceptable cardiac testing (e.g. TTE)
- Primary pulmonary hypertension
- Rheumatic heart disease
- Thrombocytosis, thrombocytopenia
- Any condition contraindicating chronic anticoagulation
- Active systemic infection
- Hypertrophic cardiomyopathy
- Cryoglobulinemia
- Uncontrolled hyperthyroidism
- Any cerebral ischemic event (strokes or TIAs) which occurred during the 6 month interval preceding the consent date
- Any woman known to be pregnant or breastfeeding, or any woman of child bearing potential who is not on a reliable form of birth regulation method or abstinence
- Life expectancy less than one year
- Current or anticipated participation in any other clinical trial of a drug, device or biologic during the duration of the study not pre-approved by Medtronic
- Known allergies or hypersensitivities to adhesives
- Known drug or alcohol dependency
- Unwilling or unable to comply fully with study procedures and follow-up

## 13. 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 be screened to confirm eligibility for enrollment with defined inclusion/exclusion criteria prior to enrollment
- Subject demographics will be collected at baseline in order to later assess possible characteristics that may influence endpoints
- A statistical analysis plan will be developed prior to analyzing data which will document all pre-specified analyses and analysis methods
- All centers and geographies will use the same version of the CIP
- All study clinicians and Medtronic personnel will be trained on their respective aspects of the study using standardized training materials
- All study clinicians will be trained on and required to follow the CIP
- An independent Clinical Events Committee (CEC) will be utilized to regularly review and adjudicate at a minimum, all system (cryoablation and [redacted]) related and all procedure related adverse events, as well as all deaths in the study.
- An independent core lab will be utilized to regularly review and adjudicate the arrhythmia component of the primary endpoint, recurrent AF/AT/AFL.
- 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 center to ensure an even distribution of total subjects across centers.
- [redacted]

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

# 14. Study Procedures

## 14.1. Schedule of Events

Data collection requirements are summarized in Table 7.

**Table 7: Study Procedures and Data Collection per Subject Visit**

| | Baseline | Cryoablation Procedure | Hospital Discharge | Repeat Ablation in Blanking | 6 week phone call | 3 Month Visit | 6 and 12 Month Visit | Repeat Ablation out of Blanking | Unscheduled Visit | Exit |
|---|---|---|---|---|---|---|---|---|---|---|
| Consent | X | | | | | | | | | |
| Inclusion/Exclusion Criteria | X | | | | | | | | | |
| Medical History | X | | | | | | | | | |
| Physical Examination | X | | | | | | | | | |
| Review Medications | X | | X | | X | X | X | | X | |
| Pregnancy Screen (if applicable)[1] | X | | | | | | | | | |
| 12-Lead ECG | X | | X | | | X | X | | X | |
| Trans-thoracic Echocardiogram (TTE)[2] | X | | | | | | | | | |
| SF-12 Health Survey and AFEQT Questionnaire | X | | | | | | X | | | |
| Trans-esophageal Echocardiogram (TEE)[3] | X | | | X | | | | | | |
| Sub-study [redacted][4] | [redacted] | | | | | [redacted] | | | | |
| Ablation Procedure Data | | X | | X | | | | X | | |
| 24h Continuous Monitoring with Holter | | | | | | | X | | | |
| Trans-telephonic monitoring | | | | | | Weekly and upon symptoms | | | | |
| Review symptoms suggestive of recurrent AF/AT/AFL | | | | | X | X | X | | X | |
| Device Deficiencies | As they occur | | | | | | | | | |
| Adverse Events (incl. AE with outcome of death) | As they occur | | | | | | | | | |
| Study Deviation | As they occur | | | | | | | | | |
| Study Exit Information | | | | | | | | | | X[5] |

[1]Female subjects of child bearing potential only
[2]Only required if data not available from within prior 6 months from consent date.
[3]TEE to assess for LA thrombus as indicated by the 2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation.
[4]Subjects need to sign the sub-study patient informed consent form [redacted] See Appendix B for additional details.
[5]A review of medications, adverse event assessment and a 12-lead ECG should be attempted if the subject exits the study outside of a study visit.

## 14.2. Role of the Sponsor

Sponsor representatives may provide support as required for the study under supervision of the Principal Investigator, including:

- Provide study training relevant and pertinent to the involvement of personnel conducting study activities and Investigator responsibilities
- Technical support during the procedures under the supervision of a study Investigator, but no data entry, shall be performed by Medtronic personnel or their representatives at centers
- Monitoring and auditing activities

## 14.3. Subject Consent

Patient informed consent (PIC) is defined as a legally effective documented confirmation of a subject's (or their legally authorized representative except in Europe) 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 PIC Form and an Authorization to Use and Disclose Personal Health Information that has been approved by the study center's IRB/MEC and signed and dated by the subject or their legally authorized representative (except in Europe). 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 (except in Europe) 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 PIC Form must have been approved by each center's IRB/MEC. Each site must also use an Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language as required by law. The PIC Form must be controlled (i.e. versioned and/or dated) to ensure it is clear which version(s) were approved by the IRB/MEC. Any adaptation of the sample PIC Form must be reviewed and approved by Medtronic and the IRB 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 course of 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 PIC Form and the Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language 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 PIC Form, to inquire about details of the study, and to decide whether or not 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 PIC Form and the Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language 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 PIC Form was accurately explained and clearly understood by the subject, and that informed consent was freely given.

In Europe and Japan, include a personally dated signature by the Principal Investigator or authorized designee responsible for conducting the informed consent process. The Principal Investigator or designee must conduct the informed consent discussion.

A copy of the PIC Form and the Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language as required by law, 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) PIC 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 PIC Form. In Europe, when a subject cannot read and/or write, an independent witness shall be present throughout the process, the written PIC Form and any other information shall be read aloud and explained to the prospective subject. The subject should "make his mark" (sign or otherwise physically mark the document so as to indicate consent) on the PIC Form as well. The PIC Form should document the method used for communication with the prospective subject and the specific means by which the prospective subject communicated agreement to participate in the study.

The original of the signed PIC Form and the Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language as required by law must be filed in the hospital/clinical chart and/or with the subject's study documents. PIC Form (in Japan, the signature page only) and the Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language as required by law 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 PIC Form and verify its completeness prior to proceeding with the procedure. In the event the Medtronic Field personnel identify a PIC 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. In Japan, only the monitor assigned to the study may be able to review the signed PIC Form prior to the study procedure.

## 14.4. Enrollment, Baseline and Pre-ablation

When a patient and the Principal Investigator or authorized designee, as required, have signed and dated the PIC Form, the patient is considered a subject enrolled in the study. The date the subject signed the PIC Form and Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language as required by law must be documented in the subject's medical records.

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:

- Trans-thoracic echocardiogram (TTE) for the collection of left atrial size, left ventricular ejection fraction, and mitral valve impairment. A repeat TTE procedure for the purpose of the study after the consent date is not required if a TTE was performed within 6 months of the consent date 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.

- Assessment of all factors specified for evaluation under Inclusion Criteria and Exclusion Criteria (Section 12)
- Demographics
- Medical history
- Physical examination
- Pregnancy screen (female subjects of child bearing potential only)
- 12-lead ECG
- Review of AF and anticoagulation medications
- SF-12 health survey and AFEQT Questionnaire
- Transesophageal Echocardiogram (TEE)
    - When performed, the TEE should occur within one day (on the day of or within the day prior to) the planned ablation procedure.
    - A TEE should be performed in all subjects with atrial fibrillation more than 48 hours in duration or of an unknown duration if adequate systemic anticoagulation has not been maintained for at least 3 weeks prior to the ablation procedure.
    - Performance of a TEE in subjects who are in sinus rhythm at the time of ablation or eligible subjects that have been in AF for 48 hours or less prior to AF ablation may be considered but is not mandatory.
    - The subject will not proceed with the study ablation procedure and will be exited from the study if a left atrial thrombus is visualized.
- [redacted] if enrolled in the sub-study (see Appendix B)

## 14.5. Procedure

Perform the pulmonary vein isolation procedure using Arctic Front Advance Cardiac CryoAblation Catheter. If needed, a Freezor *MAX* Cardiac CryoAblation Catheter may also be utilized for gap ablation to complete electrical isolation of the pulmonary veins and creation of ablation lines between the inferior vena cava and the tricuspid valve. The Investigator is to perform the procedure according to the procedural steps in this CIP and the Instructions for Use for the Arctic Front Advance and Freezor *MAX* Cardiac CryoAblation Catheters. Appropriate sedation and venous access should be attained at the Investigator's standard practice according to their institution's pre-established procedures/guidelines at the time of the procedure. Current recommendations for anticoagulation are found in the 2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation[1], 2014 Focused Update on the Canadian Cardiovascular Society Guidelines for the Management of Atrial Fibrillation[18] and Guidelines for indications and procedural techniques of catheter ablation.[19]

Only the Medtronic FlexCath sheath family should be used with the Arctic Front Advance Cardiac CryoAblation Catheter. The use of other sheaths may damage the device. The Investigator may choose compatible guidewires and mapping catheters at his or her discretion.

### 14.5.1. Esophageal Visualization and Temperature Monitoring

a. Ensure an esophageal temperature monitor is used for each cryoablation application. Cease cryoablation if the temperature reaches ≤15°C.

### 14.5.2. Peri-procedural Anticoagulation

a. 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.
b. 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.
c. Administration of protamine following ablation to reverse heparin should be considered.

### 14.5.3. Diaphragm Movement

a. Continuous phrenic nerve pacing must be performed for all right sided pulmonary vein cryoapplications and should be considered for all cryoapplications. Additional methods of phrenic nerve monitoring are recommended.

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[18] Verma, A, MD, 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.
[19] Okumura. Guidelines for indications and procedural techniques of catheter ablation. *Japan Circulation Society*. 2012.

### 14.5.4. Balloon Pulmonary Vein (PV) Cryoablation

a. Every effort consistent with subject welfare should be made to treat all PVs or their anomalous equivalents.

b. The Arctic Front Advance will be advanced into the left atrium over the Achieve catheter or guidewire and inflated. Once inflated, the catheter will be tracked over the Achieve catheter or guidewire and positioned at the entrance of the PV.

c. Assess the positioning, contact and occlusion of the PV by the catheter's balloon by injection of contrast material, ultrasound imaging, or other technique. Reposition as needed.

d. Each pulmonary vein should be minimally assessed for entrance block and, where assessable, exit block to demonstrate electrical isolation.

e. It is recommended that the Investigator use cryoapplications of three (3) minutes each. Once PV isolation has been achieved, one (1) additional application of three (3) minutes at the same PV should be performed; however, it is up to the operator's discretion to assess application time and necessity of a bonus freeze given factors such as time to isolation of first application, temperature of first application, risk of collateral damage, etc.

f. Upon the Investigator's assessment of procedure completion, Isoproterenol and/or adenosine may be used to assess pulmonary vein isolation.

### 14.5.5. Other Ablations during Index Procedure

a. Ablation of the cavotricuspid isthmus, with the goal of achieving bi-directional isthmus block, is required for subjects with a history of typical atrial flutter or inducible cavotricuspid isthmus dependent atrial flutter. It is recommended to attempt an induction of cavotricuspid isthmus dependent atrial flutter if the subject does not have a history of this arrhythmia. Any commercially released catheter deemed appropriate for the procedure may be used.

b. Left atrial non-PVI ablations including but not limited to, ablation of linear lesions, complex fractionated electrograms or non-PV triggers will be treated as a primary endpoint failure. Ablation using RF in the left atrium will be treated as a primary endpoint failure.

c. Additional right atrial ablations may be performed if clinically necessary.

### 14.5.6. Cardioversion

a. Electrical or pharmacological cardioversion to sinus rhythm must be attempted following the PVI portion of the procedure if sinus rhythm wasn't restored.

### 14.5.7. Procedure Documentation

During the procedure the Investigator will document the following:

- Catheters used (i.e. Arctic Front Advance, Freezor *MAX* and Achieve Mapping Catheter, etc.)
- Minimum temperature for each cryoapplication
- Minimum esophageal temperature for each PV
- Duration of each cryoapplication
- Vein location for each cryoapplication (e.g. right superior PV)
- Use of phrenic nerve pacing or other phrenic nerve monitoring technique for each cryoapplication, specifically those cryoapplications surrounding the RS and RI PVs
- Demonstrated electrical block and, if real-time signals are available, time to isolation
- Adjunctive catheters, mapping or visualization devices, sedation type, procedure information, esophageal temperature, ACT, cardioversion use and fluoroscopy time will be collected

## 14.6. 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.[1,21,22]

## 14.7. 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. Up-titration of the dose is allowed only in the 90 day post-procedure blanking period.

Information regarding medications prescribed for anticoagulation or to treat atrial arrhythmias, including the medication name, purpose for use, start and stop dates, and route of administration, will be collected from subject enrollment through study exit.

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

- Subjects are allowed to remain on Class I or III antiarrhythmic medications at the historic maximum ineffective dose (on prior to the ablation procedure) 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 after the 90 day post-procedure blanking period will be treated as a primary endpoint failure.
- Remaining on a dose higher than the historic maximum ineffective dose (on prior to the ablation procedure) after the 90 day post-procedure blanking period will be treated as a primary endpoint failure.

All medications are permitted in the study with the exception of investigational drugs that may confound the study results.

### 14.8. Permissible Repeat Cryoablations

Pulmonary vein isolation using Arctic Front Advance following the same procedure described in 14.5 is allowed one time in the 90 day post-procedure blanking period. Right atrial ablations may be performed using any catheter deemed appropriate for the procedure.

Left atrial ablations of non-PV triggers, complex fractionated electrograms and ablation of linear lesions will be treated as a primary endpoint failure. Ablation using RF in the left atrium will be treated as a primary endpoint 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 cryoballoon ablation procedure date.

### 14.9. Cardioversions

Electrically and pharmacologically cardioverting the subject to sinus rhythm is allowed within the 90 day post-procedure blanking period at the discretion of the Investigator.

### 14.10. Scheduled Follow-up Visits

After receiving notice of 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 8 and are based on days after the index ablation procedure.

**Table 8: Follow-up Schedule**

| Occurrence/ Visit | Window (Calculated days after the ablation procedure) | | |
|---|---|---|---|
| | Window Start | Target | Window End |
| Enrollment/Baseline | -30 days | -15 days | Day 0 |
| Index Cryoablation Procedure | Day 0 | Day 0 | Day 0 |
| 6 week phone call | 35 days | 39 days | 42 days |
| 3 month office | 91 days | 91 days | 121 days |
| 6 month office | 165 days | 180 days | 195 days |
| 12 month office | 365 days | 365 days | 395 days |

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

### 14.10.1. Six Week Phone Call

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

### 14.10.2. Three Month Office Visit

- Review medications
- Adverse event assessment
- Review symptoms suggestive of recurrent AF/AT/AFL
- 12-lead ECG
    - Send to the core lab
- Review the TTM system and begin transmitting weekly and upon symptoms

### 14.10.3. Six Month Office Visit

- Review medications
- Adverse event assessment
- Review symptoms suggestive of recurrent AF/AT/AFL
- 12-lead ECG
    - Send to the core lab
- 24h continuous monitoring with Holter
    - Send to the core lab
- SF-12 Health Survey and AFEQT Questionnaire

### 14.10.4. Twelve Month Office Visit

- Review medications
- Adverse event assessment
- Review symptoms suggestive of recurrent AF/AT/AFL
- 12-lead ECG
    - Send to the core lab
- 24h continuous monitoring with Holter
    - Send to the core lab
- SF-12 Health Survey and AFEQT Questionnaire

## 14.11. 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
    - Send to the core lab

## 14.12. Holter and TTM Management

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 then be sent back to the center after they have been worn by the subject. The core lab will be responsible for adjudication of atrial arrhythmias for the primary objective of the study. The core lab will manage maintenance, calibration and tracking of the Holters.

Holter distribution logs will be provided to European centers. The logs must be maintained and updated when Holters are received and returned to the core lab.

Market-released TTMs will be distributed by a core lab to centers after activation has occurred. All subjects will transmit weekly and symptomatic ECGs via the TTM system following their 3 month office visit. The TTM system will be sent back to the core lab at the end of the study. The core lab will be responsible for adjudication of atrial arrhythmias for the primary objective of the study. The core lab will manage maintenance, calibration and tracking of the TTMs.

TTM distribution logs will be provided to European centers. The logs must be maintained and updated when TTMs are received and returned to the core lab.

## 14.13. 12 lead Electrocardiograms

Market-released 12-lead ECG machines will be distributed by a core lab to centers after activation has occurred. All 12-lead ECGs starting with the one occurring at the 3 month office visit will be sent to the core lab. The 12-lead ECG machine will be sent back to the core lab at the end of the study. The core lab will be responsible for adjudication of atrial arrhythmias for the primary objective of the study. Copies of additional source documents may be requested. The core lab will manage maintenance, calibration and tracking of the 12-lead ECG machine.

12-lead ECG distribution logs will be provided to European centers. The logs must be maintained and updated when 12-lead ECG machines are received and returned to the core lab.

## 14.14. [redacted]

Follow Appendix B if the subject is enrolled in the sub-study [redacted]

## 14.15. Assessment of Efficacy

The primary efficacy objective is based on the ECG data collected as discussed in Section 18.

## 14.16. 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 18.

## 14.17. Recording Data

The study will collect data using Oracle Clinical, an electronic data management system for clinical studies. Centers will enter data onto case report forms (CRFs) within an Oracle Clinical database. The Holter/TTM/12-lead ECG core lab will also enter data onto CRFs within a separate Oracle Clinical database.

Data reported on the CRFs shall be derived from source documents, which may include worksheets, quality of life questionnaires, patient medical records and ECG data. These source documents must be created and maintained by the center personnel. Further detail on data management is provided in Section 20.2.

## 14.18. 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. In countries following ISO 14155:2011, prior approval for study deviations will be reported to local authorities and ethics boards per local requirements. If the deviation affects subject's rights, safety and well-being, or the scientific integrity of the study, prior approval from ethics board and/or competent authority is also required, depending on local legislations. 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). A study deviation is not required if a subject misses a weekly TTM transmission.

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/MEC as well as Medtronic within five (5) working days. In Japan, the deviation must be immediately reported to Head of Medical Institute (HOMI), to the Ethics Board via the HOMI, and to Medtronic. Reporting of study deviations should comply with IRB/MEC policies, local laws and/or regulatory agency requirements and must be reported to Medtronic as soon as possible upon the center becoming aware of the deviation. Refer to Investigator Reports, Section 20.5.2, for specific deviation reporting requirements and timeframes for reporting to Medtronic and/or regulatory bodies.

Medtronic is responsible for analyzing deviations, assessing their significance, and identifying any additional corrective and/or preventive actions (e.g. amend the CIP, conduct additional training, and 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.

## 14.19. Subject Withdrawal or Discontinuation

A subject can withdraw from the study or the [redacted] sub-study at any time. If the subject wishes to exit from the study (i.e. the subject revokes consent), the center is required to document the reason for exit on an eCRF. In addition, centers shall follow the regulations set forth by their IRB/MEC. It is recommended to follow the subject until all ongoing device and/or procedure-related adverse events are resolved or unresolved with no further actions planned. For countries following ISO, permission may be requested to follow-up with the subject outside of the study due to withdrawal based on problems related to the study device safety or performance. Following 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 study exit include:

- Subject lost to follow-up
- Subject did not meet inclusion/exclusion criteria after consent and did not undergo an ablation procedure
- An Arctic Front Advance 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

The following information is required to be collected at study exit:

- Reason for exit must be documented on the eCRF and in the subject's medical record

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.

# 15. Risks and Benefits

## 15.1. 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 residual risks associated with the Arctic Front Advance and Freezor *MAX* Cardiac CryoAblation Catheters have been found to be acceptable and have been mitigated to the fullest extent possible. The potential benefits related to the use of the Arctic Front Advance and Freezor *MAX* Cardiac CryoAblation Catheters have been determined to outweigh any potential risks. Neither device has been recalled.

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 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):

- Anemia-deficiency of red blood cells or of hemoglobin in the blood resulting in weariness
- Anxiety-a feeling of worry, nervousness, or unease
- Back pain-pain felt in the lower or upper back
- Bronchitis, cough, pneumonia-inflammation of the lungs can be caused by a virus or bacteria
- 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
- 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
- Complications associated with contrast agents-adverse effects of contrast agents used during the procedure (e.g. allergic reaction or radio contrast nephropathy)
- Complications associated with medications commonly utilized during the procedure-known risks of medications commonly used during the procedure (e.g. narcotics, anxiolytics, other pain medications, anti-vasospasm agents)
- Complications at catheter insertion site in the groin:
    - AV fistula-an abnormal connection between an artery and a vein (i.e., cause by needle insertion through the femoral artery and vein)
    - Hematoma/Bruising-a collection of blood in the tissue surrounding the catheter insertion site
    - Infection-localized redness, heat swelling and pain at the catheter insertion site
    - Pain-discomfort at the catheter insertion site that can range from mild to severe

  - Pseudoaneurysm-a collection of blood in the tissue surrounding the catheter insertion site due to ongoing leaking of blood from a blood vessel
  - Significant bleeding-blood loss from the catheter insertion site requiring surgery or transfusion of 2 or more units of packed red blood cells (PRBCs)

- Coronary artery spasm, vasospasm-constriction of a blood vessel
- Death-a complication or deterioration of health ultimately leading to a patient's death
- Diarrhea-feces are discharged from the bowels frequently and in a liquid form
- Difficulty swallowing-narrowing of the esophagus
- Digestive discomfort-pain in the abdomen
- Dissection of a blood vessel-tear within the wall of a blood vessel
- Dizziness, lightheadedness-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.
- Endocarditis –inflammation of the inner surface of the heart
- Esophageal injury –damage to your swallowing tube, atrio-esophageal fistula - abnormal passageway between the heart and esophagus, hematemesis (vomiting blood)
- Fatigue-extreme tiredness
- Fever-abnormally high body temperature
- Gastroparesis- delayed gastric emptying
- Headache-pain in the head
- Heart rhythm disturbances-disruption of normal heart rate or rhythm e.g. atrial flutter, tachycardia, bradycardia
- Hemothorax–collection of blood around the lungs
- Hiccups-involuntary spasm of the diaphragm and respiratory organs
- Hypertension-high blood pressure
- Hypotension-low blood pressure
- Hypoxia-deficiency in the amount of oxygen reaching the tissues
- Injury to lung- (e.g. bronchial lesion, hemoptysis, constriction, pulmonary hemorrhage, bronchia fistula)

- Mild skin discomfort or irritation-redness sensitivity of the skin cause during or after the procedures (e.g. electrodes used with the ECG and Holter recorder might cause mild skin discomfort or irritation or some skin discomfort following electrode removal or tape removal).
- Nausea-a sensation of unease and discomfort in the upper stomach with an urge to vomit
- Perforation of a blood vessel or cardiac tissue-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 that surrounds the heart
- Nerve injury– e.g. damage to the phrenic nerve that controls breathing
- Pleural effusion–collection of extra fluid around the lungs
- Pulmonary edema-excess fluid in the lungs
- Pulmonary hypertension-high blood pressure that affects the arteries in the lungs and the right side of the heart
- Pulmonary vein hematoma-trauma to the pulmonary vein
- Pulmonary vein stenosis –blockage in the blood vessels takes blood from the lungs to the heart
- Pneumothorax – collapsed lung
- Renal dysfunction-kidneys fail to adequately filter waste products from the blood
- Bleeding e.g. bleeding into the retroperitoneal space
- Right sided heart failure-right side of the heart is not pumping blood to the lung normally
- Shivering-body shaking
- Shortness of breath-difficulty breathing
- ST elevation-the ST segment of an ECG is abnormally high above the baseline
- Sore throat-pain in the throat
- Urinary infection-an infection in the urinary system
- Vascular complications requiring surgery-damage to an artery (e.g. femoral) or vein requiring surgical repair
- Vasovagal reaction-reflex of the involuntary nervous system that causes the heart to slow down and blood pressure drops
- Vomiting-forceful expulsion of stomach contents through the mouth and/or nose

## 15.2. Risk Minimization

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

- Selecting qualified Investigators and training study personnel on the CIP
- Requiring that Investigators be actively involved in the procedure and follow-up of the subjects who undergo a study procedure
- Providing guidelines for subject selection and evaluation
- Requiring that subjects be followed at regular intervals following the ablation procedure to monitor for recurrence of atrial arrhythmias and to assess for adverse events

### 15.3. Potential Benefits

The Arctic Front Advance Cardiac CryoAblation Catheter may reduce or eliminate persistent atrial fibrillation in subjects; however, some subjects may not receive this benefit. The information gained from the study could result in improved management of atrial fibrillation.

### 15.4. 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. Cryoablation therapy offers the opportunity to reduce the episodes of atrial fibrillation and therefore reduce the subject's risk of stroke and symptoms.

In the United States, there are no ablation catheters approved to treat subjects with persistent atrial fibrillation. If successful, the STOP Persistent AF study could demonstrate meaningful therapeutic benefit in this underserved population.

In Japan, there are limited options for physicians to choose for the treatment of persistent atrial fibrillation. If successful, the STOP Persistent AF study could demonstrate meaningful therapeutic benefit in this underserved population.

In Canada and Europe, the Arctic Front Advance ablation catheters are approved to treat subjects with persistent atrial fibrillation. If successful, the STOP Persistent AF study could confirm meaningful therapeutic benefit in this underserved population.

## 16. Adverse Event and Device Deficiencies Assessment

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 geographies are taken into account for the collection and reporting of safety information.

## 16.1. Adverse Event and Device Deficiency Definitions

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.

**Table 9: 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<br><br>NOTE 1: This definition includes events related to the investigational medical device or the comparator.<br>NOTE 2: This definition includes events related to the procedures involved.<br>NOTE 3: For users or other persons, this definition is restricted to events related to investigational medical devices.<br>(ISO 14155:2011, 3.2) |
| Adverse Device Effect (ADE) | Adverse event related to the use of an investigational medical device<br><br>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.<br>NOTE 2: This definition includes any event resulting from an error use or from intentional misuse of the investigational medical device.<br>(ISO 14155:2011, 3.1) |
| Device Deficiency (DD) | Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.<br><br>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 that encompasses cryoablation. |
| Cryoablation system related | An Adverse Event that results from the presence or performance (intended or otherwise) of the cryoablation system (including the Arctic Front Advance, Freezor MAX, FlexCath Sheath, Achieve Mapping Catheter, CryoConsole, Manual Retraction Kit) |
| [redacted] | [redacted] |
| Cardiovascular related | An Adverse Event relating to the heart and the blood vessels or the circulation. |

| **Seriousness** | |
|---|---|
| Serious Adverse Event (SAE) | Adverse event that<br>a) led to death,<br>b) led to serious deterioration in the health of the subject, that either resulted in:<br>1) a life-threatening illness or injury, or<br>2) a permanent impairment of a body structure or a body function, or<br>3) in-patient or prolonged hospitalization (>24 hours), or<br>4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,<br>c) led to fetal distress, fetal death or a congenital abnormality or birth defect<br><br>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.<br>(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.<br>(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.<br>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** | |

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

## 16.2. Adverse Events

For the purposes of the study, the following Adverse Events will be collected starting at the time of signing the PIC Form through the duration of the subject's participation in the study:

- All procedure related AEs
- All system related AEs (cryoablation and [redacted])
- All cardiovascular related AEs
- All Serious Adverse Events (SAEs), regardless of relatedness

Reporting of these events to Medtronic will occur on an Adverse Event (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 9 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

Subject deaths are also required to be reported. Refer to section 16.6 for Subject Death collection and reporting requirements.

## 16.3. Device Deficiencies

Device deficiency (DD) information will be collected throughout the study and reported to Medtronic. 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 AEs/DDs that require immediate reporting, initial reporting may be done by contacting the study sponsor per the sponsor contact information.

## 16.4. Processing Updates and Resolution

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, is unresolved with no further actions planned, the subject exits the study or until study closure, whichever occurs first.

In the event that a subject is exited from the study prior to study closure, all efforts should be made to continue following the subject until all unresolved procedure or system related adverse events, as classified by the Investigator, are resolved or they are unresolved with no further actions planned.

At the time of study exit, all adverse events with an outcome of "Unresolved, further actions or treatment planned" must be reviewed and an update to the original AE must be reported. At a minimum, if there are no changes to the description, relatedness, test and procedures or actions taken, the outcome must be updated to reflect "Unresolved at time of study closure."

## 16.5. Reporting of Adverse Events and Device Deficiencies

All reported adverse events and device deficiencies 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/device deficiency 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 and device deficiencies that could have led to a SADE will be completed according to local regulatory requirements. Refer to Section 20.5 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 G. This is a list of adverse events related to the Arctic Front Advance CryoAblation Catheter or procedure that have been observed in previous studies and may be experienced by subjected. This list may help to assess if an adverse event is unexpected in nature.

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 below:

**Table 10: Adverse Event Classification Responsibilities**

| What is classified? | Who classifies? | Classification Parameters |
|---|---|---|
| Relatedness | Investigator | Cryoablation procedure related, Cryoablation system related, [redacted], Cardiovascular related |
| | Sponsor | Cryoablation procedure related, Cryoablation system related, [redacted] |
| 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 |

An independent Clinical Events Committee (CEC) will at a minimum, review all system (cryoablation and [redacted]) related and all procedure related adverse events, as well as all deaths and provide a final adjudication and death classification.

**Adverse Event and Device Deficiency Reporting Requirements**

Regulatory reporting of AEs/DDs will be completed according to local regulatory requirements. It is the responsibility of the Investigator to abide by any additional AE/DD reporting requirements stipulated by the IRB/MEC responsible for oversight of the study. Investigators should report Serious Adverse Events to Medtronic immediately after the Investigator learns of the event. In case that the Adverse Event is related to a market-released device used during the study, post market surveillance is also applicable and the Investigator is responsible for immediate reporting of the product compliant via the regulator channels for market-released products.

**Table 11: Adverse Event and Device Deficiency Report Requirements**

| Serious Adverse Events (SAEs) | |
|---|---|
| **Investigator submit to:** | |
| Medtronic | **Europe**: Immediately after the Investigator first learns of the event or of new information in relation with an already reported event. *(ISO 14155 and local law)*<br>**Japan**: All serious, adverse events must be reported, whether or not there exists a |

| | |
|---|---|
| | cause and effect relationship with the investigational device. The Principal Investigator shall immediately report all serious, adverse events to the sponsor, unless emergency reports are stipulated as being unnecessary in such documents as the CIP and investigational device summary. The Principal Investigator shall promptly submit a detailed written report after submitting and emergency report (MHLW Ordinance 36, 2005 Article 68)<br><br>**All geographies:** Report to the sponsor, without unjustified delay, all serious adverse events. (ISO 14155:2011) |
| MEC/IRB | **All geographies:** Submit to MEC/IRB per local reporting requirement. |
| Regulatory Authorities | **All geographies:** Submit to regulatory authority per local reporting requirement. |
| HOMI | **Japan**: All serious, adverse events must be reported, whether or not there exists a cause and effect relationship with the investigational device. The principal shall immediately report in writing all serious, adverse events to HOMI. In this case, the Principal Investigator shall identify serious, unpredictable adverse device effects out of the reported serious, adverse events. (MHLW Ordinance 36, 2005 Article 68) |
| **Sponsor submit to:** | |
| Investigators | **Japan**: All SAEs classified as reportable events follow the applicable reporting requirements. (MHLW Ordinance 36, 2005 Article 28) |
| MEC/IRB | **All geographies:** Submit to MEC/IRB per local reporting requirement.<br><br>**Japan**: in the case where there is a prior agreement with the IRB and HOMI, all SAEs classified as reportable events follow the applicable reporting requirements. (MHLW Ordinance 36, 2005 Article 28) |
| Regulatory Authorities | **All geographies:** Submit to regulatory authority per local reporting requirement.<br><br>**Japan**: All SAEs classified as reportable events follow the applicable reporting requirements. (Pharmaceutical Affairs Law Enforcement Regulations, Article 274.2, 275) |
| HOMI | **Japan**: All SAEs classified as reportable events follow the applicable reporting requirements. (MHLW Ordinance 36, 2005 Article 28) |
| **Serious Adverse Device Effects (SADEs)** | |
| **Investigator submit to:** | |
| Medtronic | **Europe:** Immediately after the Investigator first learns of the event or of new information in relation with an already reported event. (ISO 14155 and local law)<br><br>**Japan**: the Principal Investigator shall immediately report to the sponsor. (MHLW Ordinance 36, 2005, Article 68)<br><br>**All other geographies:** Submit as soon as possible after the Investigator first learns of |

| | |
|---|---|
| | the event, and per local requirements |
| MEC/IRB | **All geographies:** Submit to MEC/IRB 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 |
| HOMI | **Japan**: The Principal Investigator shall immediately report to HOMI. (MHLW Ordinance 36, 2005 Article 68) |
| **Sponsor submit to:** | |
| Investigator | **Japan**: All SADEs classified as reportable events follow the applicable reporting requirements. (MHLW Ordinance 36, 2005 Article 28) |
| MEC/IRB | **All geographies:** Submit to MEC/IRB per local reporting requirement.<br>**Japan**: in the case where there is a prior agreement with the IRB and HOMI, all SADEs classified as reportable events follow the applicable reporting requirements. (MHLW Ordinance 36, 2005 Article 28) |
| Regulatory authorities | **Canada**: All SADEs on the patient, the user or any other person: these must be reported by Medtronic to the regulatory 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))<br>**Japan**: All SADEs classified as reportable events follow the applicable reporting requirements. (Pharmaceutical Affairs Law Enforcement Regulations, Article 273, 275)<br>**All geographies:** Submit to regulatory authority per local reporting requirement. |
| HOMI | **Japan**: All SAEs classified as reportable events follow the applicable reporting requirements. (MHLW Ordinance 36, 2005 Article 28) |
| **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)) |

| | |
|---|---|
| | **Europe:** Immediately after the Investigator first learns of the event or of new information in relation with an already reported event.<br><br>**Japan**: The Principal Investigator shall immediately report to the sponsor. (MHLW Ordinance 36, 2005 Article 68) |
| MEC/IRB | **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))<br><br>**All geographies:** Submit to MEC/IRB per local reporting requirement. |
| Regulatory authorities | **Europe:** Submit to regulatory authority per local reporting requirement. |
| HOMI | **Japan**: The Principal Investigator shall immediately report to HOMI. (MHLW Ordinance 36, 2005 Article 68) |
| **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))<br><br>**Japan**: Report to the Principal Investigator per reporting requirements (MHLW Ordinance 36, 2005 Article 28) |
| MEC/IRB | **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))<br><br>**Japan**: Report to the IRB per reporting requirements in the case where there is a prior agreement with the IRB and HOMI. (MHLW Ordinance 36, 2005 Article 28) |
| 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))<br><br>**Canada:** All USADEs on the patient, the user or any other person; these must be reported by Medtronic to the regulatory 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 Device Regulations, SOR/98-282; Mandatory Problem Reporting 59(1) , 59(2), 60 (1))<br><br>**Europe:** Submit to regulatory authorities per local reporting requirement.<br><br>**Japan**: Report to the regulatory authorities per reporting requirements. (Pharmaceutical Affairs Law Enforcement Regulations, Article 274.2, 275) |

| | |
|---|---|
| HOMI | **Japan**: Report to HOMI per reporting requirements (MHLW Ordinance 36, 2005 Article 28) |
| **Adverse Device Effects** | |
| **Investigator submit to:** | |
| Medtronic | **Europe:** Immediately after the Investigator first learns of the effect. *(ISO 14155 and local law)*<br>**All other geographies:** Submit in a timely manner after the Investigator first learns of the effect. |
| MEC/IRB | **All geographies:** Submit to MEC/IRB per local reporting requirement. |
| Regulatory authorities | **All geographies:** Submit to regulatory authority per local reporting requirement. |
| **Sponsor submit to:** | |
| MEC/IRB | **All geographies:** Submit to MEC/IRB per local reporting requirement. |
| Regulatory authorities | **All geographies:** Submit to regulatory authority 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 to regulatory authority per local reporting requirement. |
| MEC/IRB | **All geographies:** Submit to MEC/IRB per local reporting requirement. |
| **Sponsor submit to:** | |
| Regulatory authorities | **All other geographies:** Submit to regulatory authority per local reporting requirement. |
| **Device Deficiencies and SADE Potential** | |
| **Investigator submit to:** | |
| Medtronic | **Europe:** Immediately after the Investigator first learns of the deficiency or of new information in relation with an already reported deficiency.<br>**All geographies:** Report to the sponsor, without unjustified delay, all device |

| | |
|---|---|
| | deficiencies that could have led to a serious adverse device effect (ISO 14155:2011) |
| Regulatory authorities | **All geographies:** Submit to regulatory authority per local reporting requirement. |
| MEC/IRB | **All geographies:** Submit to regulatory authority per local reporting requirement. |
| **Sponsor submit to:** | |
| MEC/IRB | **All geographies:** Submit to EC/IRB per local reporting requirement. |
| Regulatory authorities | **Canada:** Any Device Deficiency that:<br>• 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 to the Regulator within 10 days from the date Medtronic becomes aware.<br>or<br>• could do so were it to reoccur. These must be reported by Medtronic to the Regulator within 30 days from the date Medtronic becomes aware.<br>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 Device Regulations, SOR/98-282; Mandatory Problem Reporting 59(1) , 59(2), 60 (1))<br>**Europe:** Submit to regulatory authorities per local reporting requirement.<br>**All geographies:** Submit to regulatory authority 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. |
| MEC/IRB | **All geographies:** Submit to Ethics Committee per local reporting requirement. |
| Regulatory authorities | **All geographies:** Submit to regulatory authority per local reporting requirement. |

## 16.6. Subject Death

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

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)

### 16.6.1. Death Classification and Reporting

Sufficient information will be required in order to properly classify the subject's death. The Investigator shall classify each subject death per the following definitions:

- 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.

## 16.7. Product Complaint Reporting

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 clinical 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 medical device distributed by Medtronic, regardless whether they are related to intended use, misuse or abuse of the product. Reporting must be done immediately and via the regular channels for market-released products.

Medtronic will notify the regulatory authorities (e.g. FDA) 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

The Investigator and Medtronic must abide by the reporting requirements shown in Section 20.5.

## 17. Data Review Committees

At regular intervals, an independent Clinical Events Committee (CEC) will review and adjudicate, at a minimum, all system (cryoablation and [redacted]) related and all procedure related 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. Associated imaging studies (i.e. CT, MRI, x-ray, etc.) may be requested, if available, for all serious adverse events with possible relatedness to the system or procedure listed in Section 18.3.2 to support adjudication. 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/MECs and regulatory authorities, if required.

# 18. Statistical Design and Methods

## 18.1. General Considerations

Two analysis cohorts have been defined for this study:

1. PMA-S cohort (US/Canada/Europe cohort) – subjects from US, Canada, and Europe centers
2. PMDA cohort (US/Canada/Europe/Japan cohort) –subjects from US, Canada, Europe, and Japan centers

Analysis methods are detailed for all objectives in sections 18.1- 18.5. The same methods will be used for both the PMA-S cohort, and also the PMDA cohort. The estimated sample sizes are 150 subjects for the PMA-S cohort, and 165 subjects for the PMDA cohort. The PMDA cohort will have a slight increase in statistical power given 165 subjects will be utilized versus 150.

The Statistical Analysis Plan (SAP) will be created prior to data analysis and include a comprehensive description of the statistical methods to be included in study reports. Any change to the data analysis methods described in the CIP will require an amendment only if it changes a principal feature of the CIP. Any other change to the data analysis methods described in the CIP, and the justification for making the change, will be described in the clinical study report. Medtronic employees or their designated representatives will perform all statistical analyses.

## 18.2. Analysis Timing

### 18.2.1. PMA-S Submission

At the completion the last 12 month visit from the enrolled and treated US, Canada and Europe subjects, a PMA-S will be submitted to the FDA. Study data from the Japanese centers will not be included in the PMA-S submission but will be made available.

### 18.2.2. PMDA Submission

At the completion the last 12 month visit from the enrolled and treated Japan subjects, a report will be submitted to Japan PMDA. Study data from all enrolled and treated subjects (US, Canada, Europe, and Japan) will be included.

## 18.3. Primary Objectives

### 18.3.1. Primary Efficacy Objective

Demonstrate an acceptable efficacy success rate at 12 months after the pulmonary vein isolation (PVI) ablation procedure.

**Hypothesis**

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

Ho: PS ≤ 40%

Ha: PS > 40%

Where PS is the probability of treatment success at 12 months.

**Endpoint Definition**

Treatment success is defined as freedom from treatment failure. Treatment failure is defined as any of the following components:

- Acute procedural failure
- Documented AF/AT/ AFL on Holter/TTM/12-lead ECG after the 90 day blanking period
  - Minimum of 30 seconds on Holter/TTM and 10 seconds on 12-lead ECG
- A reablation for the treatment of recurrent AF/AT/AFL after the 90 day blanking period
- Class I or III antiarrhythmic drug (AAD) dose increase from the historic maximum ineffective dose (prior to the ablation procedure) or initiation of a new Class I or III AAD after the 90 day blanking period. Note: remaining on the same pre-ablation dose or decreased dose, or re-initiation of a previously failed or not tolerated Class I or III AAD after the 90 day blanking is not considered a failure. Subjects are allowed to remain on Class I or III antiarrhythmic medications at the historic maximum ineffective dose (on prior to the ablation procedure) after the 90 day post-procedure blanking period.
- Ablation using RF in the left atrium

Blanking period is defined as the first 90 days after the index ablation procedure. Recurrences of atrial arrhythmias during the blanking period will not be counted in the determination of the first clinical failure for the primary endpoint. Within the blanking period, recurrent arrhythmias can be managed with antiarrhythmic drugs, cardioversion or one cryo re-ablation procedure of the pulmonary veins. Titration of Class I and III antiarrhythmic medications are allowed during the blanking period.

Acute procedural failure is defined as:

- Inability to isolate all accessible targeted pulmonary veins (minimally assessed for entrance block and, where assessable, exit block) during the index procedure
- Left atrial non-PVI ablations including but not limited to, ablation of linear lesions, complex fractionated electrograms or non-PV triggers

**Analysis Methods**

The probability of a subject achieving effectiveness success at 12 months (365 days) will be estimated using survival analysis, the Kaplan-Meier method. The standard error will be approximated using Greenwood's formula. A two-sided 95% log-log confidence interval for the probability will be constructed.

For every treated subject, day 0 is defined as the day of the index cryoablation procedure. For subjects with treatment failure, the survival date will be set to the date of the treatment failure. For subjects without treatment failure through 12 months, those subjects will be censored at the last study contact date

recorded on CRF which may include the last study visit, the exit date, or death date. If a subject without a treatment failure is lost to follow-up, the censoring date will be set to the last known study visit date.

For the component of the endpoint, documented AF/AT/AFL, if this documentation resulted from rhythm monitoring occurring at the 12-month visit within the 12-month visit window, the date of recurrence will be set to 365 days from the study ablation procedure so that these events will be counted as treatment failures in the 12-month Kaplan-Meier analysis.

**Performance Requirements**

If the lower bound of the 95% confidence interval at 12 months is greater than the performance goal of 40%, the objective will be considered met.

**Rationale for Performance Criteria**

The choice of twelve month follow-up and acceptable success rate of 40% performance criteria was selected based on the 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, provides recommendations for success rates in clinical trials. The recommendation for evaluating the efficacy of a treatment for persistent AF is as follows: "*If minimum chronic success rate is selected as an objective effectiveness endpoint for a clinical trial, we recommend that the minimum chronic acceptable success rate for persistent AF at 12-month follow-up is 40%.*"[1]

Additionally, there is mounting evidence in published literature on the use of catheter ablation in the treatment of persistent AF. Table 12 displays a summary of published literature where the publications reported on utilizing Arctic Front and Arctic Front Advance catheters for the treatment of patients with persistent AF. The summary includes results published as manuscripts in peer reviewed medical journals. The search criteria were publications on studies where the therapy was the use of the Cryoballoon for a PVI-only approach for persistent AF. There were variations in endpoint definitions and use of antiarrhythmic medications in the reported studies, but on average the data support the criteria from the 2012 HRS/EHRA/ECAS Expert Consensus Statement. A weighted average was calculated at the bottom of the table, resulting in an average efficacy rate of 59.3%. None of the studies utilized weekly TTMs, so due to the additional arrhythmia monitoring, the point estimate for this study has been set to 54%. The weighted average lower 95% confidence bound is 43.8%, and in combination of additional arrhythmia monitoring, support the lower confidence bound OPC of 40%.

**Table 12: Summary of Published Literature on Catheter Ablation for Persistent AF**

| Reference | Design | Sites | Subjects | Subject Monitoring (When/How) | Efficacy Arrhythmia Assessment | 12M Efficacy* | Off AADs? | Acute Procedural Success |
|---|---|---|---|---|---|---|---|---|
| Aytemir K, et al<br>J Interv Card Electrophysiol 2013;38(3):187-195. [i] | Prospective, observational, consecutive patients, PVI-only | 1 | 48 | ECG and 24hr Holter @ 3M,6M,12M and symptomatic event recorder | AF > 30s | 0.62 (0.47, 0.76) | YES | 99.50% |
| Ciconte G, et al<br>Heart Rhythm. 2014; 12(1):60-6. [ii] | Prospective, consecutive patients, PVI-only | 3 | 63 | ECG and 24hr Holter @ 1M,3M,6M,12M | Any AF/AT > 30s | 0.60 (0.47, 0.72) | YES | 100% |
| Ferrero-De Loma-Osorio A., et al<br>J. Intervent. Card. Electrophysiol. August 1 2013;37(2):189-196. [iii] | Prospective, consecutive patients, PVI-only | 1 | 23 | 3M and every 6 thereafter (72h Holter + ECG) | AF > 30s | 0.49 (0.27, 0.69) | YES | 96.80% |
| Jackson N, et al Heart Lung Circ 2012;21(8):427-432. [iv] | Consecutive patients, PVI-only | 1 | 61 | 3M,6,12 (unspecified duration Holter + ECG) | AF > 30s | 0.59 (0.46, 0.71) | YES | 97.70% |
| Kojodjojo P, et al<br>Heart 2010;96(17):1379-1384. [v] | Prospective, consecutive patients | 1 | 34 | 3M,6,12 and every 6 thereafter (24h Holter + ECG +symptomatic event recorder) | Any AF/AT > 30s | 0.48 (0.30, 0.65) | YES | 83% |
| Kubala M, et al<br>Clin Electrophysiol 2011;34(7):837-843. [vi] | Prospective, consecutive patients, PVI-only | 1 | 33 | ECG and 24hr Holter @ 1M,3M,6M,12M and symptomatic event recorder | AF > 30s | 0.52 (0.34, 0.69) | YES | Not reported |
| Malmborg H,et al<br>Europace 2013;15(11):1567-1573. [vii] | Prospective, randomized, PVI-only | 1 | 15 | ECG @ 3M,6,12 and 7 day Holter @ 6M,12M | AF > 30s | 0.60 (0.32, 0.84) | NO | 98% |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Neumann T, et al<br>J Am Coll Cardiol 2008;52(4):273-278[viii] | Prospective, consecutive patients, PVI-only | 3 | 53 | 7 day Holter @ 3M,6M,9M,12M | AF > 30s | 0.42 (0.28, 0.56) | YES | 97% |
| Schmidt M, et al<br>Int J Cardiol 2013;167(1):114-120[ix] | Consecutive patients, PVI-only | 3 | 44 | ECG and 72hr Holter @ 1M,3M,6M,9M,12M and symptomatic event recorder | AF or Flutter >30s | 0.77 (0.62, 0.89) | YES | 100% |
| Schmidt M, et al<br>Clin Res Cardiol 2012;101(10):777-785. [x] | Prospective, consecutive patients, PVI-only | 1 | 33 | ECG and 72hr Holter @ 1M,3M,6M,9M,12M and symptomatic event recorder | AF > 30s | 0.70 (0.51, 0.84) | NO | 98.40% |
| Lemes C, et al<br>Europace. 2015 May 19. [Epub ahead of print].[xi] | Retrospective, PVI-only | 2 | 49 | Holter and ECG and telephonic interviews @ 3M,6M,12M | Any AF/AT > 30s | 0.69 (0.57, 0.83) | YES | 100% |
| **Weighted average (weights based on study sample size)** | | | | | | **59.3% (43.8, 74.4%)** | | |

*Confidence interval calculated with binomial Fisher's exact methods

**Sample Size Calculation**

For the US/Canada/Europe cohort, 150 treated subjects affords 90% power based on the following assumptions:

- One analysis at 12-months
- 12-month efficacy rate = 54%
- OPC = 40% at 12-months
- Overall alpha = 0.025, one-sided
- 10% attrition through 12 months
- Binomial exact methods

Table 12 summarizes the published literature of 12-month efficacy rates for Cryoballoon PVI ablation. The summary estimates 12-month efficacy to be 59.3%. Due to more stringent endpoint definition, increased monitoring, and the potential for publication bias, this study protocol assumes a 12 month efficacy rate of 54% for the sample size calculation. With 150 enrolled and treated subjects, minus an assumed 10% attrition rate, the expected number of subjects with 12 months of follow-up at the final analysis is 135.

For the US/Canada/Europe/Japan cohort, 165 treated subjects affords 92% power to test the primary endpoint based on the same assumptions. With 165 enrolled and treated subjects, minus an assumed 10% attrition rate, the expected number of subjects with 12 months of follow-up at the final analysis is 148.

**Determination of Subjects/Data for Analysis**

All enrolled subjects who have the Arctic Front Advance Cardiac CryoAblation Catheter inserted into vasculature will be included.

**Sensitivity Analyses**

A sensitivity analysis will be conducted to estimate the potential impact of subjects with less than 12 months of follow-up at the final analysis. The mortality rate in this patient population is anticipated to be low. The total assumed attrition rate through one year is 10%. Because the primary endpoint will be tested using survival methods, all treated subjects are included in the primary analysis, and therefore no subjects will have complete missing data. For subjects that exit early, a tipping point analysis will be conducted to estimate the potential impact of subjects with less than 12-months of follow-up. These subjects will be defined as subjects with partial data. The tipping point analysis methods will be as follows. For each subject with less than 12-months of follow-up, each subject will be set to treatment failure (failure date set to date of study exit). The 12-month Kaplan-Meier estimate will be re-calculated with the earliest (closest to index ablation) sequentially added to the Kaplan-Meier analysis, and the results presented in table format. The tipping point will be defined as the number of additional failures in which the 40% OPC is crossed by the lower 95% confidence bound.

### 18.3.2. Primary Safety Objective

Demonstrate an acceptable safety profile of the pulmonary vein isolation (PVI) ablation procedure.

**Hypothesis**

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

Ho: $P_S \geq 13\%$

Ha: $P_S < 13\%$

Where $P_S$ is the probability of a safety event through 12 months.

**Endpoint Definition**

A primary safety event is defined as a serious procedure-related or serious system-related adverse event including the following:

- Transient ischemic attack (within 7 days of ablation procedure)
- Cerebrovascular accident (within 7 days of ablation procedure)
- Major bleeding that requires transfusion (within 7 days of ablation procedure)
- Cardiac perforation, tamponade or pericardial effusion (within 7 days of ablation procedure)
- Pulmonary vein stenosis (>75% reduction within 12-months of ablation procedure)
- Myocardial infarction (within 7 days of ablation procedure)
- Phrenic nerve injury (unresolved at 12-months)
- Atrio-esophageal fistula (within 12-months of ablation procedure)
- Death (within 7 days of ablation procedure)

**Analysis Methods**

The probability of a safety event at 12 months (365 days) will be estimated using survival analysis, the Kaplan-Meier method. The standard error will be approximated using Greenwood's formula. A two-sided 95% log-log confidence interval for the probability will be constructed.

For every treated subject, day 0 is defined as the day of the index cryoablation procedure. For subjects with a safety event, the survival date will be set to the date of the safety event. For subjects without a safety event, those subjects will be censored at the last study contact date recorded on CRF which may include the last study visit, the exit date, or death date. If a subject without a safety event is lost to follow-up, the censoring date will be set to the last known study visit date.

For subjects with a repeat ablation within 12 months, the start of the survival analysis will not reset. Day 0 will remain the day of the index cryoablation procedure. Safety events related to the repeat ablation procedure occurring on or prior to 365 days post the index cryoablation procedure will be counted as safety events and count against the primary safety objective.

**Performance Requirements**

If the upper bound of the two-sided 95% confidence interval at 12 months is less than the performance goal of 13%, the objective will be considered met.

**Determination of Subjects/Data for Analysis**

All enrolled subjects who have the Arctic Front Advance Cardiac CryoAblation Catheter inserted into vasculature will be included.

**Sample Size Calculation**

For the US/Canada/Europe cohort, 150 treated subjects affords 86% power based on the following assumptions:

- One analysis at 12-months
- 12-month safety rate = 5%
- Clinically important difference = 8% (i.e., if the safety rate of the cryoballoon in this population is 5%, the study will have adequate power to demonstrate a difference from 13%)
- Overall alpha = 0.025, one-sided
- 10% attrition

With 150 enrolled and treated subjects, minus an assumed 10% attrition rate, the expected number of subjects with 12 months of follow-up at the final analysis is 135.

For the US/Canada/Europe/Japan cohort, 165 treated subjects affords 93% power to test the primary endpoint based on the same assumptions. With 165 enrolled and treated subjects, minus an assumed 10% attrition rate, the expected number of subjects with 12 months of follow-up at the final analysis is 148.

**Rationale for Performance Criteria**

The safety endpoint definition is based on the Guidance for Industry and FDA Staff[20]. The estimated safety rate of 5% was selected based on current rate observed in the STOP AF Post Approval Study (PAS). Table 13 summarizes the safety event rate in STOP AF PAS. The safety event rate is 2.3% in STOP AF PAS based on the 2015 FDA Annual Report. The study was not complete and follow-up was ongoing at the time of the 2015 annual report. Therefore the event rate may be slightly higher when the study is completed due to additional events reported, the persistent AF population being studied under this protocol has further advanced AF disease, and therefore the estimated rate for the STOP Persistent AF study has been estimated to be 5%. The OPC of 13% is based on the meaningful clinical difference of 8% (i.e., if the safety rate of the cryoballoon in this population is 5%, the study will have adequate power to demonstrate a difference from 13%)

[20] Clinical Study Designs for Percutaneous Catheter Ablation for Treatment of Atrial Fibrillation. January 9, 2004.

**Table 13: Safety Event Rate in STOP AF PAS**

| Study | Observed Safety Event Rate[1] |
|---|---|
| STOP AF PAS (n=347)[21] | 8 safety events in 8 subjects<br>Safety event rate = 2.3%<br>PNI Unresolved at 12 months (3)<br>Cerebrovascular accident (1)<br>Pericardial Effusion (1)<br>Cardiac tamponade (1)<br>PV Stenosis (1)<br>Incision site hematoma (1) |

[1]Based on the primary safety endpoint definition in this STOP Persistent AF protocol

[21] 60 Month Interim Post Approval Study Status Report. PMA P100010/R Arctic Front Cardia CryoAblation System. STOP AF PAS. Version 2, 10DEC2015.

## 18.4. Secondary Objective

The secondary objective, Quality of Life, will be evaluated to gain additional information about the performance of the Arctic Front Advance Cardiac CryoAblation catheter.

There are three hypotheses tested in the objective, hypothesis tests for AFEQT questionnaire, the physical component score of the SF-12 questionnaire, and the mental component score of the SF-12 questionnaire. A Hommel multiple testing procedure will be utilized to maintain an overall type I error rate of 0.025 for this objective[22].

The Hommel procedure is a stepwise procedure and will be implemented following the below.

The three hypothesis will be defined as H(1), H(2), and H(3). For each of the hypotheses, p-values will be calculated and sorted $p(1) < p(2) < p(3)$. The decision rule to accept or reject each hypothesis will follow the step-up algorithm, where $\alpha=0.025$:

Step 1: If $p(3) > \alpha$, accept H(3) and go to Step 2, otherwise reject all hypotheses and stop

Step 2: If $p(2) > \alpha/2$, accept H(2) and go to Step 3, otherwise reject all remaining hypotheses and stop

Step 3: If (1) $\alpha/2 < p(2) \leq 2\alpha/3$ and $p(1) \leq \alpha/2$ or (2) $p(1) \leq \alpha/3$, reject H(1); otherwise accept H(1)

### 18.4.1. Secondary Objective: Quality of Life - Atrial Fibrillation Effect on QualiTy-of-life (AFEQT) and SF-12 Questionnaires

Demonstrate an improvement in quality of life between baseline and 12 months as measured by the AFEQT and SF-12 questionnaires.

#### 18.4.4.1 Atrial Fibrillation Effect on QualiTy-of-life (AFEQT)

**Hypothesis**

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

Ho: $\Delta AFEQT = 0$

Ha: $\Delta AFEQT > 0$

Where $\Delta AFEQT$ is the change in AFEQT score from baseline to 12 months.

**Endpoint Definition**

[22] Hommel, G. A stagewise rejective multiple test procedure based on a modified Bonferroni test. *Biometrika* 1988; 75, 383-386.

The AFEQT questionnaire will be utilized for this objective. The questionnaire is an atrial fibrillation specific health-related quality of life questionnaire to assess the impact of AF on a subject's life. The overall score ranges from 0 – 100, with 0 corresponds to complete disability and 100 corresponds to no disability.

**Analysis Methods**

Change in AFEQT score is defined as 12-month AFEQT score minus baseline AFEQT score. Change in AFEQT scores will be assessed utilizing a one-sample t-test. A two-sided 95% confidence interval will be calculated based on the t-distribution.

Additionally, summary statistics (e.g. mean, SD, median, range) and graphical methods will be used to summarize the change in AFEQT scores from baseline through 12 months.

**Performance criteria**

If the p-value from the one-sample t-test after adjusting for the Hommel procedure is < 0.025, the objective will be considered met.

**Determination of Subjects/Data for Analysis**

All enrolled subjects who have the Arctic Front Advance Cardiac CryoAblation Catheter inserted into vasculature and have completed baseline and 12 month questionnaires will be included.

**Additional Analyses**

The AFEQT questionnaire has three subscale scores, Daily Activities Subscale, Treatment Concern, and Treatment satisfaction. Each subscale ranges from 0 – 100, where 0 corresponds to low quality-of-life and 100 corresponds to high quality of life.

Change in AFEQT subscale score is defined as 12-month AFEQT subscale score minus baseline AFEQT subscale score. A two-sided 95% confidence interval will be calculated based on the t-distribution.

#### 18.4.4.2 Medical Outcome Study Short Form-12 (SF-12 )

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

Ho: $\Delta SF\text{-}12_{mental} = 0$ Ho: $\Delta SF\text{-}12_{physical} = 0$

Ha: $\Delta SF\text{-}12_{mental} > 0$ Ha: $\Delta SF\text{-}12_{physical} > 0$

Where $\Delta SF\text{-}12_{mental}$ is the change in ΔSF-12 mental score from baseline to 12 months, and $\Delta SF\text{-}12_{physical}$ is the change in ΔSF-12 physical score from baseline to 12 months

**Endpoint Definition**

The Medical Outcome Study Short Form-12 (SF-12) questionnaire will be utilized for this objective. The SF-12 questionnaire is a health-related quality of life questionnaire to evaluate the subject's mental and physical performance. Physical and mental health component scores are calculated using responses to 12 questions with a response range from 0 – 100, with 0 corresponds to lowest level of health and 100 indicates highest level of health.

**Analysis Methods**

Change in SF-12 component score is defined as 12-month SF-12 score minus baseline SF-12 score. Change in SF-12 scores will be assessed utilizing a one-sample t-test. A two-sided 95% confidence interval will be calculated based on the t-distribution.

Additionally, summary statistics (e.g. mean, SD, median, range) and graphical methods will be used to summarize the change in SF-12 scores from baseline through 12 months.

**Performance criteria**

If the p-value from the one-sample t-test after adjusting for the Hommel procedure is < 0.025, the objective will be considered met.

**Determination of Subjects/Data for Analysis**

All enrolled subjects who have the Arctic Front Advance Cardiac CryoAblation Catheter inserted into vasculature and have completed baseline and 12 month questionnaires will be included.

## 18.5. Ancillary Objectives

Ancillary objectives been defined to provide additional information about the performance of the Arctic Front Advance Cardiac CryoAblation Catheter. No hypotheses are defined for regulatory or labeling purposes.

[redacted]

[redacted]

[redacted]

[redacted]

vasculature will be included.

[redacted]

[redacted]

## 19. Ethics

### 19.1. 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 Ethics Board/Institutional Review Board (IRB)/Medical Ethics Committee (MEC)/Head of Medical Institution (HOMI) before initiating a study, continuing review of an ongoing study by an Ethics Board, and obtaining and documenting the freely given informed consent of a subject before initiating the study.

The study was designed to reflect the GCP principles outlined in ISO 14155:2011 and other international clinical requirements outlined below. These include the protection of the rights, safety and well-being of human subjects, controls to ensure the scientific conduct and credibility of the clinical investigation and the definition of responsibilities of the sponsor and Investigators. In accordance with ISO standard, the sponsor shall avoid improper influence on, or inducement of, the subject, monitor, any Investigator(s) or other parties participating in or contributing to the clinical investigation. All Investigators shall avoid improper influence on or inducement of the subject, sponsor, monitor, other Investigator(s) or other parties participating in or contributing to the clinical investigation. The ISO standard also informed study design in the areas of device deficiency reporting and risk evaluation, with the exception (to Section 6.4 of the ISO standard) that only those Adverse Events (AEs) which are cardiovascular, serious, system (cryoablation and [redacted]) related and procedure related will be collected. This ensures any AEs which could potentially be relevant will be collected. There is a second exemption (to Section 18.1 of the ISO standard) that device accountability will not be performed in Europe or Canada and only upon package opening in the US (full device accountability will take place in Japan starting with distribution).

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. In Europe, the study will also be conducted in accordance with the Declaration of Helsinki 2013. For all geographies, the principles of the Declaration of Helsinki have been implemented through the patient informed consent (IC) process, Ethics Board/IRB/MEC approval, study training, clinical trial registration, preclinical testing, risk-benefit assessment and publication policy.

Ultimately, all centers in 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)
- 21 CFR Part 54 (Financial Disclosure by Clinical Investigators)
- The procedures described with in this CIP
- Local Ethics Board requirements

All participating geographies will make study data available to the regulatory body such as FDA or competent authority 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 the United States, US FDA 21 CFR Parts
    - 50: Protection of Human subjects, 56: Institutional Review Boards and 812: Investigational Device Exemptions
- In Europe, Declaration of Helsinki 2013, the Competent Authority requirements, the Medical Device Directive (MDD) 93/42/EEC and ISO 14155:2011 with the exception stated earlier in this Section
- In Canada, the Medical Devices Regulations, Mandatory Medical Device Problem Reporting 59(1), 59(2), 60(1)
- In Japan, the study will be conducted in compliance with MHLW Ordinance No. 36, 2005 and related laws and regulations

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:

- US Food and Drug Administration (FDA) or regulatory authority
- Pharmaceuticals and Medical Device Agency (PMDA) (if applicable)
- Medtronic
- Principal Investigators (where required by local law)
- An independent IRB/MEC

Similarly, approval of subsequent revisions to the CIP is required at each study center from the above mentioned groups prior to implementation of the revised CIP at that center.

# 20. Study Administration

## 20.1. 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 in order 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 PIC 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/MEC approval and review of the study, maintenance of records and reports, and review of source documents against subject CRFs. 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 particular center.

## 20.2. 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, TTMs and 12-lead 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:

- Time of isolation of the cryoablation catheter
- 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
- Database generate patient reference ID

When copies or print-outs of the source documents are made, center personnel must sign and date any copies or printouts of original source documents with a statement that this is complete and true reproduction of the original source document.

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/MEC review and regulatory inspection by providing direct access to source data/documents.

## 20.3. Confidentiality

All records and other information about subjects participating in the study will be treated as confidential. See Section 20.2 for further information.

## 20.4. 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 MEC or IRB

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/MEC as required by the committee. CIP amendments will also be reported to and approved by the FDA.

## 20.5. Record Retention

### 20.5.1. Investigator Records

The Investigator, or in Japan, the record keeping manager at the study center is responsible for the preparation and retention of the records cited below. All of the below records, with the exception of case history records and 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/MEC, sponsor, monitor, FDA, local regulatory agencies and the Investigator that pertains to the investigation, including required reports
- Subject's case history records, including:
- Signed and dated PIC Form signed by subject (In Europe and Japan, signed by subject, subject's legally authorized representative except in Europe and Investigator. In Japan, it is acceptable to retain only the signature page with the version number of the PIC Form.)
- 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) and subject identification logs (Europe only)
- List of investigation centers
- Financial disclosure of Investigators
- Device Disposition Logs (US and Japan)
- All approved versions of the CIP, PIC, and Investigator's Brochure/Report of Prior Investigation Summary
- Signed and dated Clinical Trial Agreement and Investigator Statement
- Current curriculum vitae (signed and dated in Europe) of Investigators and key members of investigation center team (Europe only)
- Documentation of delegated tasks
- Blank case report forms (Europe only)
- IRB/MEC approval documentation. Written information that the Investigator or other study staff, when member of the IRB/MEC, did not participate in the approval process. Approval documentation must include the IRB/MEC composition, in Europe and 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/MEC)
- Any other records that FDA and local regulatory agencies require to be maintained
- Final Study Report including the statistical analysis

### 20.5.2. Investigator Reports

The Investigator is responsible for the preparation (review and signature) and submission to the sponsor of all eCRFs, adverse events, device deficiencies, deaths, and any deviations from the CIP. If any action is taken by an IRB/MEC with respect to this clinical study, copies of all pertinent documentation must be forwarded to Medtronic in a timely manner. Reports are subject to inspection and to the retention requirements as described above for Investigator records.

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

**Table 14: Investigator reports applicable for all geographies per Medtronic requirements**

| Report | Submit to | Description/Constraints |
|---|---|---|
| Withdrawal of IRB/MEC approval | Sponsor and Relevant Authorities | The Investigator must report a withdrawal of approval by the reviewing IRB/MEC of the Investigator's part of the investigation within 5 working days. |
| Study deviations | Sponsor and IRB/MEC | Any deviation from the clinical investigational plan shall be recorded together with the explanation of the deviation. Notice of deviations from the CIP to protect the life or physical well-being of a subject in an emergency shall be given as soon as possible, but no later than 5 working days after the emergency occurred. Except in such emergency, prior approval is required for changes in the plan or deviations. |
| Final report | Sponsor IRB/MECs Relevant Authorities | This report must be submitted within 3 months of study completion or termination. |
| Refer to Section16 for adverse event, complaint, and device deficiency reporting. | | |

**Table 15: Additional Investigator reports applicable to the United States**

| Report | Submit to | Description/Constraints |
|---|---|---|
| Withdrawal of IRB/MEC approval (either suspension or termination) | Sponsor | The Investigator must report a withdrawal of approval by the reviewing IRB/MEC of the Investigator's part of the investigation within 5 working days. *(21 CFR 812.150(a)(2))* |
| Progress report | Sponsor and IRB/MEC | The Investigator must submit this report to the sponsor and IRB/MEC at regular intervals, but in no event less than yearly. *(21 CFR 812.150 (a)(3))*. |

| | | |
|---|---|---|
| Study deviations | Sponsor and<br>IRB/MEC | 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. If the deviation may affect the scientific soundness of the plan or the rights, safety and welfare of the subjects, the deviation must be approved by Medtronic, the IRB/MEC, and the FDA/applicable regulatory authorities. If the deviation does not affect these issues then only Medtronic must approve it. *(21 CFR 812.150(a)(4))* |
| Failure to obtain informed consent prior to investigational device use | Sponsor and<br>IRBs/MECs | If an Investigator uses a device without obtaining informed consent, the Investigator shall report such use within 5 working days after device use. *(21 CFR 812.150(a)(5))* |
| Final report | Sponsor<br>IRBs/MECs<br>Relevant Authorities | This report must be submitted within 3 months of study completion or termination of the investigation or the Investigator's part of the investigation. *(21 CFR 812.150(a)(6))* |
| Other | IRB/MEC and FDA | An Investigator shall, upon request by a reviewing IRB/MEC, FDA or any other regulatory agency, provide accurate, complete, and current information about any aspect of the investigation. *(21 CFR 812.150(a)(7))* |

**Table 16: Investigator reports applicable to Europe**

| Report | Submit to | Description/Constraints |
|---|---|---|
| Withdrawal of IRB/MEC approval | Sponsor | Report if required by local law. |
| Progress Report | Sponsor and<br>IRB/MEC | Provide if required by local law or IRB/MEC. |
| Study Deviations | Sponsor and<br>IRB/MEC | Any deviation from the CIP shall be recorded together with an explanation for the deviation. Deviations shall be reported to the sponsor who is responsible for analyzing them and assessing their significance.<br>Note: When relevant, ethics committees, competent authorities or the appropriate regulatory bodies should be informed. *(ISO 14155:2011)* |
| Failure to obtain informed consent | Sponsor and<br>IRBs/MECs | Informed consent shall be obtained in writing and documented before a subject is enrolled into the clinical investigation. *(ISO 14155:2011)* |

**Table 17: Investigator reports applicable to Japan**

| Report | Submit to | Description/Constraints |
|---|---|---|
| Co-Investigator/ Clinical Trial Collaborator List | HOMI | When the principal Investigator assigns important parts of the clinical trial duties to co-Investigators and/or clinical trial collaborators, he or she shall prepare a list of the assigned duties and the individual performing the assigned duties, submit the list to the HOMI on the list, and receive the appointments of such individuals. (MHLW Ordinance 36, 2005 Article 63) |
| Study Deviations | Sponsor and HOMI | The Investigator may implement a deviation from, or a change in, the protocol to eliminate an immediate hazard(s) to study subjects without prior Ethics Board approval. In this case, the Investigator shall immediately submit to the sponsor, the HOMI, and to the Ethics Board via the HOMI, the description and reason for the deviation and the proposed revision to the protocol, if one is necessary, to receive agreement. All deviations, regardless of the reason, shall be submitted to the sponsor. (MHLW Ordinance 36, 2005 Article 66) |
| Summary of the Clinical Study Status | HOMI | The principal Investigator shall submit a summary of the clinical study status to the HOMI in writing once a year, or more frequently if requested by the Ethics Board, to receive the continuation review by the institutional review board. (MHLW Ordinance 36, 2005 Article 68) |
| Premature Termination or Suspension of the Clinical Investigation | HOMI | When the principal Investigator discontinues or suspends the clinical study, he or she shall promptly notify the HOMI thereof in writing, and explain in detail in writing the discontinuation or suspension. (MHLW Ordinance 36, 2005 Article 69) |
| Completion of the Clinical Investigation | HOMI | When the clinical study is completed, the principal Investigator shall notify the HOMI thereof in writing and report on a summary of the clinical study results in writing. (MHLW Ordinance 36, 2005 Article 69) |

### 20.5.3. Sponsor Records

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

- All correspondence which pertains to the investigation
- Investigational Device Disposition Logs (US and Japan)
- Signed Investigator Trial Agreements, financial disclosure of Investigators and current signed and dated (Europe only) curriculum vitae of principal Investigator and key members of the investigation center team (as required by local law), delegated task list
- All approved versions of the PIC Form, and other information provided to the subjects and advertisements, including translations

- Copies of all IRB/MEC approval letters and relevant IRB/MEC correspondence and IRB/MEC voting list/roster/letter of assurance
- Names of the institutions in which the clinical study will be conducted
- Regulatory authorities correspondence, notification and approval as required by national legislation
- Insurance certificates (where requested by the IRB/MEC)
- Names/contact addresses of monitors
- Monitoring visit reports and follow-up letters
- Statistical analyses and underlying supporting data
- Final report of the clinical study
- All approved versions of the Clinical Investigation Plan and study related reports, Investigator's Brochure/Report of Prior Investigation Summary
- Study training records for center personnel and Medtronic personnel involved in the study
- Hospital names and evidence of hospital existence (i.e. Web page address of the institution, hospital pamphlet, etc.) and the name of the HOMI
- Any other records that local regulatory agencies require to be maintained

### 20.5.4. Sponsor Reports

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

**Table 18: Sponsor reports for the United States**

| Report | Submit to | Description/Constraints |
|---|---|---|
| Withdrawal of IRB/MEC approval | Investigators, IRB/MEC, FDA, and relevant authorities | Notification within five working days. (21 CFR 812.150(b)(2)) |
| Withdrawal of FDA approval | Investigators, IRB/MEC, and relevant authorities | Notification within five working days. (21 CFR 812.150(b)(3)) |
| Investigator List | FDA | Submit at 6-month intervals, a current list of the names and addresses of all Investigators participating in the investigation. (21 CFR 812.150(b)(4)) |
| Progress Reports | IRB/MEC and FDA | Progress reports will be submitted at least annually. (21 CFR 812.150(b)(5), 812.36(f) |

| Report | Submit to | Description/Constraints |
|---|---|---|
| Recall and device disposition | Investigators,<br>Head of Institution,<br>IRB/MEC,<br>relevant authorities, and<br>FDA | Notification within 30 working days and will include the reasons for any request that an Investigator return, repair, or otherwise dispose of any devices. (21 CFR 812.150(b)(6)) |
| Failure to obtain informed consent | FDA | Investigator's report will be submitted to FDA within five working days of notification. (21 CFR 812.150(b)(8)) |
| Final report | Investigators,<br>IRB/MEC,<br>Regulatory authorities upon request, and FDA | Medtronic will notify FDA within 30 working days of the completion or termination of the investigation. A final report will be submitted to the FDA, Investigators, and IRBs/MECs within six months after completion or termination of this study. (21 CFR 812.150(b)(7)) |
| Study deviation | Investigators | Ensure that all deviations from the Clinical Investigation Plan are reviewed with the appropriate clinical Investigator(s), are reported on the case report forms and the final report of the clinical investigation.<br>Center specific study deviations will be submitted to Investigators periodically. |
| Other | IRB, FDA | Accurate, complete, and current information about any aspect of the investigation. (21 CFR 812.150(b)(10)) |

**Table 19: Sponsor reports for Canada**

| Report | Submit to | Description/Constraints |
|---|---|---|
| Premature termination or suspension of the clinical investigation | Investigators, IRB/MEC,<br>Relevant authorities, and<br>Head of the Institution | Provide prompt notification of termination or suspension and reason(s). |
| Recall and device disposition | Investigators,<br>Head of Institution,<br>IRB/MEC,<br>relevant authorities, and<br>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. |

| Report | Submit to | Description/Constraints |
|---|---|---|
| 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.<br>Center specific study deviations will be submitted to Investigators periodically. |
| Device Deficiency | Health Canada | Any DD that:<br>a. 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 to the Regulator within 10 days from the date Medtronic becomes aware.<br>or<br>○ could do so were it to reoccur. These must be reported by Medtronic to the Regulator within 30 days from the date Medtronic becomes aware. |

**Table 20: Sponsor reports for Europe**

| Report | Submit to | Description/Constraints |
|---|---|---|
| Premature termination or suspension of the clinical investigation | Investigators,<br>IRB/MEC,<br>Relevant authorities and<br>Head of the Institution | Provide prompt notification of termination or suspension and reason(s). (ISO 14155:2011) |
| Withdrawal of IRB/MEC approval | Investigators,<br>Head of Institution,<br>IRB/MEC and<br>relevant authorities | Investigators, IRBs/MECs will be notified only if required by local laws or by the IRB/MEC. |
| Withdrawal of CA approval | Investigators,<br>Head of Institution,<br>IRB/MEC, and<br>relevant authorities | Investigators, IRBs/MECs will be notified only if required by local laws or by the IRB/MEC. |
| Progress Reports | IRB/MEC and<br>regulatory authorities | This will be submitted to the IRB/MEC only if required by the IRB//MEC). |

| Report | Submit to | Description/Constraints |
|---|---|---|
| Final report | Investigators,<br>IRB/MEC, and<br>Regulatory authorities upon request | For studies with centers complying to ISO 14155:<br>• The Investigator shall have the opportunity to review and comment on the final report.<br>• If a clinical Investigator does not agree with the final report, his/her comments shall be communicated to the other Investigator(s).<br>• The coordinating Investigators shall sign the report. If no coordinating Investigator is appointed, then the signature of the principal Investigator in each center should be obtained. (ISO 14155:2011) |
| Study deviation | Investigators | Ensure that all deviations from the Clinical Investigation Plan are reviewed with the appropriate clinical Investigator(s), are reported on the case report forms and the final report of the clinical investigation. (ISO 14155:2011)<br>Center specific study deviations will be submitted to Investigators periodically. |

**Table 21: Sponsor reports for Japan**

| Report | Submit to | Description/Constraints |
|---|---|---|
| Premature termination or suspension of the clinical investigation | HOMI<br>PMDA | When the sponsor suspends or discontinues the clinical trial, he or she shall promptly notify the heads of all the medical institutions and regulatory authorities thereof and the detailed reason therefor in writing. (MHLW Ordinance 36, 2005 Article 32) |
| Suspension of development of investigational device | HOMI<br>PMDA | When the sponsor decides not to attach the documents concerning clinical trial records collected in the clinical trial to the authorization application, he or she shall promptly notify the heads of all the medical institutions other facilities engaged in the clinical trial thereof and the detailed reason therefor in writing. (MHLW Ordinance 36, 2005 Article 32) |
| Investigator List | HOMI<br>PMDA | The sponsor shall beforehand submit the list of Investigators to PMDA and HOMI. (MHLW Ordinance 36, 2005 Article 10, Pharmaceutical Affairs Law Enforcement Regulations, Article 269, 275)<br>The sponsor shall submit the list of Investigators to PMDA and HOMI when making any changes in the list. (MHLW Ordinance 36, 2005 Article 51, Pharmaceutical Affairs Law Enforcement Regulations, Article 270, 275) |
| Important information concerning the quality, efficacy, and safety of the investigational device | Investigators<br>HOMI<br>PMDA | When new, important information is obtained, the sponsor shall revise the Investigator's brochure. In addition, prior to revising the Investigator's brochure, the sponsor shall report the information to the principal Investigator, HOMI, and regulatory authorities. (MHLW Ordinance 36, 2005 Article 28) |

| Report | Submit to | Description/Constraints |
|---|---|---|
| Clinical Trial Report | PMDA upon request | The sponsor shall prepare, according to the procedure, a clinical study report that summarizes the results, etc., of a clinical study when it is completed or discontinued. (MHLW Ordinance 36, Article 33) |
| Study deviation | Investigators<br>HOMI as<br>necessary | Ensure that all deviations from the Clinical Investigation Plan are reviewed with the appropriate clinical Investigator(s), are reported on the case report forms and the final report of the clinical investigation. (ISO 14155:2011) Center specific study deviations will be submitted to Investigators quarterly. When the monitor confirms deviation as a result of monitoring, the monitor shall notify the principal Investigator and, as necessary, the HOMI thereof. The monitor shall also request for appropriate measures to be taken to prevent such deviation in the future. (MHLW Ordinance 36, 2005 Article 30) |

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 the study.

After closure of the study Medtronic will archive records and reports indefinitely.

## 20.6. Publication and Use of Information

Publications from the STOP Persistent AF 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 STOP Persistent AF Publication Committee from the Steering Committee and/or 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 appendix, 2) develop the final Publication Plan under separate cover, 3) execute the Publication Plan, 4) oversee the publication of primary, secondary 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, Secondary and Ancillary Publications**

The Publication Committee reviews, prioritizes, and manages all publications including primary, secondary and ancillary publications. Primary and secondary publications are those that address analyses of any or all primary objectives or secondary objectives, respectively, as specified in the Clinical Investigation Plan.

An ancillary publication is any publication that does not address the study objectives identified in the Clinical Investigation Plan. 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 of 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 contributor-ship 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 STOP Persistent AF Clinical 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, IRBs/MECs and Competent Authorities 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

## 20.7. Suspension or Early Termination

### 20.7.1. 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 or not to continue the clinical study at their center.

### 20.7.2. 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

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

### 20.7.4. Procedures for Termination or Suspension

#### 20.7.4.1. Medtronic-Initiated and Regulatory Authority-Initiated

- Medtronic will promptly inform the clinical Investigators, or in Japan the HOMI, 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/MEC approval lapse, the Investigator will promptly inform the IRB/MEC/Head of Medical Institution. In Japan, the HOMI will promptly inform the Investigator and Ethics Board.
- 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

#### 20.7.4.2. Investigator-Initiated

- The Investigator will inform Medtronic and provide a detailed written explanation of the termination or suspension. In Japan, the Investigator will promptly inform the HOMI and the HOMI will inform Medtronic in writing.
- The Investigator will promptly inform the institution (where required per regulatory requirements)
- The Investigator will promptly inform the IRB/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

#### 20.7.4.3. IRB/MEC Initiated

- The Investigator, or in Japan the HOMI, will inform Medtronic and provide a detailed written explanation of the termination or suspension within 5 business days. In Japan, HOMI will also inform the Investigator.
- Subject enrollment must stop until the suspension is lifted
- Subjects already enrolled should continue to be followed in accordance with IRB/MEC policy or its determination that an overriding safety concern or ethical issue is involved
- The Investigator will inform his/her institution (where required per local requirements).
- The Investigator will promptly inform the subjects , (or legally-authorized designees or guardians except in Europe)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)

## 21. Warranty/Insurance Information

### 21.1. Warranty

Warranty information is provided in the product packaging for the Arctic Front Advance and Freezor *MAX* Cardiac CryoAblation Catheters. Additional copies are available upon request.

### 21.2. Insurance (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.

### 21.3. Insurance (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 Ethics Committee.

### 21.4. Insurance (Europe)

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

### 21.5. Insurance (Japan)

Medtronic Japan Co. Ltd. Maintains appropriate clinical trial liability insurance coverage as required under applicable laws and regulations. Documentation explaining compensation to the subjects in the event of study-related injuries will be submitted to Ethics Board. Information regarding insurance, warranty and compensation will be provided under separate cover.

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## 23. Appendices

### APPENDIX A: CRYOBALLOON SAFETY DATA LITERATURE SEARCH

The following pertains to Medtronic cryoablation products and/or related devices and includes reports identified in the scientific literature that were published from June 14, 2005 to March 15, 2015.

### Search Methodology

Three literature searches were conducted in the following databases to ensure comprehensive coverage of globally published clinical evidence for medical device products and therapies. All searches were conducted in the STN database platform.

EMBASE, published by Elsevier, contains over 11 million records with over 500,000 citations added annually. EMBASE's international journal collection contains over 5,000 biomedical journals from 70 countries.

MEDLINE is the U.S. National Library of Medicine's premier bibliographic database covering the fields of medicine, nursing, dentistry, veterinary medicine, the health care system, and the preclinical sciences.

MEDLINE contains bibliographic citations and author abstracts from more than 5,000 biomedical journals published in the United States and 80 other countries. The database contains over 15 million citations.

## Search Results

Search #1 – Medtronic Cryocath Arctic Front Brands and Models

A search was conducted for the Medtronic Cryocath Arctic Front brands and models as outlined in the table below. The search was limited to English language, human only, clinical trials, case reports, registries, editorials or meta analyses for the time period of June 14, 2005 to March 15, 2015. All notes, comments, letters, books, conference papers, practice guidelines and patents were removed from the search results. A total of 56 unique articles were located. Note that as Arctic Front Advance ST was not released to the market at the time of this search it was not included as a search term.

**Literature Search Specifications**

| | |
|---|---|
| **Search Terms** | (MEDTRONIC OR ARCTIC()FRONT) AND (ARCTIC()FRONT OR 2AF231 OR 2AF281 OR 2AF232 OR 2AF282)<br>**LIMITED TO:**<br>**Study Types:** clinical trials, meta analyses, case reports, registries, editorials |
| **Databases Searched** | MEDLINE, EMBASE |
| **Specified Timeframe** | June 14, 2005 – March 15, 2015 |

Search #2 – Medtronic Cryocath Arctic Front Advance Brands and Models

A search was conducted for the Medtronic Cryocath Arctic Front Advance brands and models as outlined in the table below. The search was limited to English language, human only, clinical trials, case reports, registries, editorials or meta analyses for the time period of June 14, 2005 to March 15, 2015. All notes, comments, letters, books, conference papers, practice guidelines and patents were removed from the search results. A total of 14 unique articles were located for this search.

**Literature Search Specifications**

| | |
|---|---|
| **Search Terms** | (MEDTRONIC OR ARCTIC()FRONT()ADVANCE) AND (ARCTIC()FRONT()ADVANCE OR 2AF234 OR 2AF284 OR 2AF283 OR 2AF233)<br>**LIMITED TO:**<br>**Study Types:** clinical trials, meta analyses, case reports, registries, editorials |
| **Databases Searched** | MEDLINE, EMBASE |
| **Specified Timeframe** | June 14, 2005 – J March 15, 2015 |

Search #3 – Cryoballoon Literature

A search was conducted for industry-wide literature on cryoballoons. The search was limited to English language, human only, clinical trials, case reports, registries, editorials or meta analyses for the time period of June 14, 2005 to March 15, 2015. All notes, comments, letters, books, conference papers, practice guidelines and patents were removed from the search results. A total of 173 unique articles were located.

**Literature Search Specifications**

| | |
|---|---|
| **Search Terms** | CRYOBALLOON OR CRYOBALLOONS<br>**LIMITED TO:**<br>**Study Types:** clinical trials, meta analyses, case reports, registries, editorials |
| **Databases Searched** | MEDLINE, EMBASE |
| **Specified Timeframe** | June 14, 2005 to March 15, 2015 |

## Final Result

Results from Search #1, Search #2 and Search #3 were combined and duplicates were removed. A total of 182 unique articles were located. Of these 182 articles, 54 articles were excluded per the following:

- 2 editorials
- 7 reviews with no new specific information
- 3 duplicates within the search
- 1 expert consensus statement
- 2 meta-analyses
- 3 were study design papers with no results
- 1 case report with no adverse events reported
- 6 did not include the Arctic Front or Arctic Front Advance cryoballoon or Atrial Fibrillation
- 4 abstracts only (unable to access full article) with no new information
- 25 articles were excluded as they did not report safety

Additional articles Medtronic was aware of or that were published after the searches were conducted were included.

**APPENDIX B: [redacted] SUB-STUDY**

*Note: Data from this sub-study will not be required to be included in standard FDA reports, including the PMA-S and final report (except as described in Section 16.5 Reporting of Adverse Events and Device Deficiencies).*

All elements of the Clinical Investigation Plan (CIP) above also apply when executing this sub-study. The elements detailed in this sub-study appendix are intended to be applied in addition to the elements described in the main CIP. [redacted]

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## APPENDIX C: DRAFT DATA COLLECTION ELEMENTS (CASE REPORT FORMS)

Draft Case Report Forms for the STOP Persistent AF 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 D: INFORMED CONSENT TEMPLATE

The Patient Informed Consent Template will be distributed under separate cover.

## APPENDIX E: PARTICIPATING INVESTIGATOR AND INSTITUTIONS

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

## APPENDIX F: IRB/MEC LIST

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

## APPENDIX G: 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 foreseeable adverse events information consists of two parts: a listing of potential adverse events associated with cryoablation therapy/procedure and adverse event rates reported in published literature for same therapy/procedure (see Appendix A). An evaluation of potentially anticipated events and reported events in literature may be used in combination with device labeling/IFU, current event reporting information, and other published data to assess for an unexpected occurrence.

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, etc.). The focus of this section is to specifically address in more detail, those events that are foreseeable due to the use, performance, and/or presence of the Arctic Front Advance CryoAblation Catheter under investigation.

Additional potential risks associated with the Arctic Front Advance CryoAblation Catheter, as well as risk minimization are discussed within Section 15.2.

Treatment required for procedure and/or 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 Arctic Front Advance CryoAblation Catheter include but are not limited to those in Table 23 and Table 24.

Table 23 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 23: Foreseeable adverse events**

| | | |
|---|---|---|
| Anemia | Feeling cold | Pseudoaneurysm |
| Anxiety | Fever | Pulmonary edema |
| Arrhythmia | Gastrointestinal discomfort | Pulmonary embolism |
| Arteriovenous fistula | Gastroparesis | Pulmonary hemorrhage |
| Atrial fibrillation | Headache | Pulmonary hypertension |
| Atrial flutter | Heart block | Pulmonary infarction |
| Atrio-esophageal fistula | Heart failure | Pulmonary infiltration |
| Back pain | Hematemesis | Pulmonary vein |

| | | |
|---|---|---|
| | | stenosis |
| Bleeding | Hematoma | Renal impairment |
| Blurred vision | Hemoptysis | Respiratory arrest or pulmonary arrest |
| Bronchial fistula | Hemothorax | Right bundle branch block |
| Bronchitis | Hiccups | Shivering |
| Bruising | Hypertension | Shortness of breath |
| Cardiac arrest or cardiopulmonary arrest | Hypotension | Sore throat |
| Cardiac perforation or cardiac vein perforation or perforation of surrounding tissue | Hypoxia | ST segment elevation |
| Cardiac tamponade | Injury to pulmonary vein e.g. pulmonary vein dissection, pulmonary vein hematoma | Stroke or cerebrovascular accident |
| Cerebral embolism | Lightheadedness | Syncope |
| Chest discomfort or pain or pressure | Lung injury | Tachycardia |
| Coronary artery spasm | Myocardial infarction | Thrombosis or thrombus |
| Cough | Nausea | Transient ischemic attack |
| Death | Nerve injury e.g. phrenic nerve injury | Urinary infection |
| Diarrhea | Neurological impairment | Vascular access site complication |

| | | |
|---|---|---|
| Dizziness | Paralysis or paresis | Vasospasm |
| Dressler's syndrome | Pericardial effusion or pericardial tamponade | Vasovagal reaction |
| Dysphagia | Pericarditis | Visual changes or visual impairment |
| Embolism | Pleural effusion | Vomiting |
| Esophageal injury/damage (including atrio-esophageal fistula) | Pneumonia | |
| Fatigue | Pneumothorax or collapse of lung | |

Table 24 is a summary of reported procedure and Arctic Front Advance Cardiac CryoAblation Catheter related adverse events reported in a Medtronic Clinical Evaluation Report for The Arctic Front Family of Catheters Recertification (Rev 1A, 19MAY2015). The observed rate is based on the study populations that included a total of 11,242 patients.

**Table 24: Arctic Front and Arctic Front Advance complications reported in literate for paroxysmal and persistent AF patients**

| Events | N=11,242<br>Rate (95% CI*) |
|---|---|
| Transient phrenic nerve injury (resolved prior to procedure end) | 4.26% (3.89-4.65%) |
| Phrenic nerve injury | 2.18% (1.92-2.47% |
| Groin hematoma | 0.58% (0.45-0.74%) |
| Pericardial effusion/pericardial tamponade | 0.53% (0.41-0.69%) |
| Pseudoaneurysm | 0.36% (0.25-0.48%) |
| Hemoptysis | 0.27% (0.18-0.38%) |
| Femoral arterio-venous fistula | 0.21% (0.14-0.32%) |

| Events | N=11,242<br>Rate (95% CI*) |
|---|---|
| Cardiac tamponade | 0.20% (0.13-0.31%) |
| Bleeding | 0.14% (0.08-0.23%) |
| Gastroparesis | 0.14% (0.08-0.23%) |
| Hematoma | 0.14% (0.08-0.23%) |
| Atrial flutter | 0.13% (0.07-0.22%) |
| Atrial tachycardia | 0.12% (0.06-0.20%) |
| Esophageal damage/ulceration | 0.12% (0.06-0.20%) |
| Transient ischemic attack | 0.12% (0.06-0.20%) |
| Stroke or cerebral vascular accident | 0.10% (0.05-0.18%) |
| Myocardial infarction | 0.05% (0.02-0.12%) |
| Atrio-esophageal fistula | 0.04% (0.01-0.10%) |
| Guidewire dissection | 0.04% (0.01-0.10%) |
| Pulmonary vein stenosis | 0.04% (0.01-0.10%) |
| ST elevation | 0.04% (0.01-0.10%) |
| Accidental femoral artery puncture | 0.03% (0.01-0.09%) |
| Inguinal aneurysm | 0.03% (0.01-0.09%) |
| Pulmonary edema | 0.03% (0.01-0.09%) |
| Difficulty swallowing/dysphagia | 0.02% (0.002-0.06%) |
| Hemothorax | 0.02% (0.002-0.06%) |
| Pericarditis | 0.02% (0.002-0.06%) |
| Pulmonary vein hematoma | 0.02% (0.002-0.06%) |

| Events | N=11,242<br>Rate (95% CI*) |
|---|---|
| Thrombosis or thrombus | 0.02% (0.002-0.06%) |
| Vasovagal reaction | 0.02% (0.002-0.06%) |
| Chest discomfort or pain or pressure | 0.01% (0.0002-0.5%) |
| Cough | 0.01% (0.0002-0.5%) |
| Death | 0.01% (0.0002-0.5%) |
| Headache | 0.01% (0.0002-0.5%) |
| Hemoptysis-clinically important | 0.01% (0.0002-0.5%) |
| Inappropriate sinus tachycardia | 0.01% (0.0002-0.5%) |
| Lightheadedness | 0.01% (0.0002-0.5%) |
| Nausea | 0.01% (0.0002-0.5%) |
| Odynophagia | 0.01% (0.0002-0.5%) |
| Pneumonia | 0.01% (0.0002-0.5%) |
| Pneumothorax or collapsed lung | 0.01% (0.0002-0.5%) |
| Pulmonary infarction | 0.01% (0.0002-0.5%) |
| Pulmonary infiltration | 0.01% (0.0002-0.5%) |
| Sinus arrest/3$^{rd}$ degree AV block | 0.01% (0.0002-0.5%) |
| Transient AV block | 0.01% (0.0002-0.5%) |

*95% CI calculated with binomial exact methods

## APPENDIX H: PRE-CLINICAL TESTING

A summary of results from pre-clinical testing with the Arctic Front Advance and Freezor *MAX* Cardiac CryoAblation Catheters is provided in the Report of Prior Investigations Summary.

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