Sponsor	*United States of America* Medtronic, Inc. 8200 Coral Sea Street NE Mounds View, MN 55112 United States of America
Local Sponsor	*Canada* Medtronic of Canada, Ltd. 99 Hereford Street Brampton, Ontario, L6Y 0R3 Canada *Europe* Medtronic, Bakken Research Center B.V. Endeplosdomein 5 6229 GW Maastricht The Netherlands *Japan* Medtronic Japan Co. Ltd. 1-2-70 Konan Minato-ku, Tokyo 108-0075 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. 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. 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).

[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]

[redacted]

8. Study Design

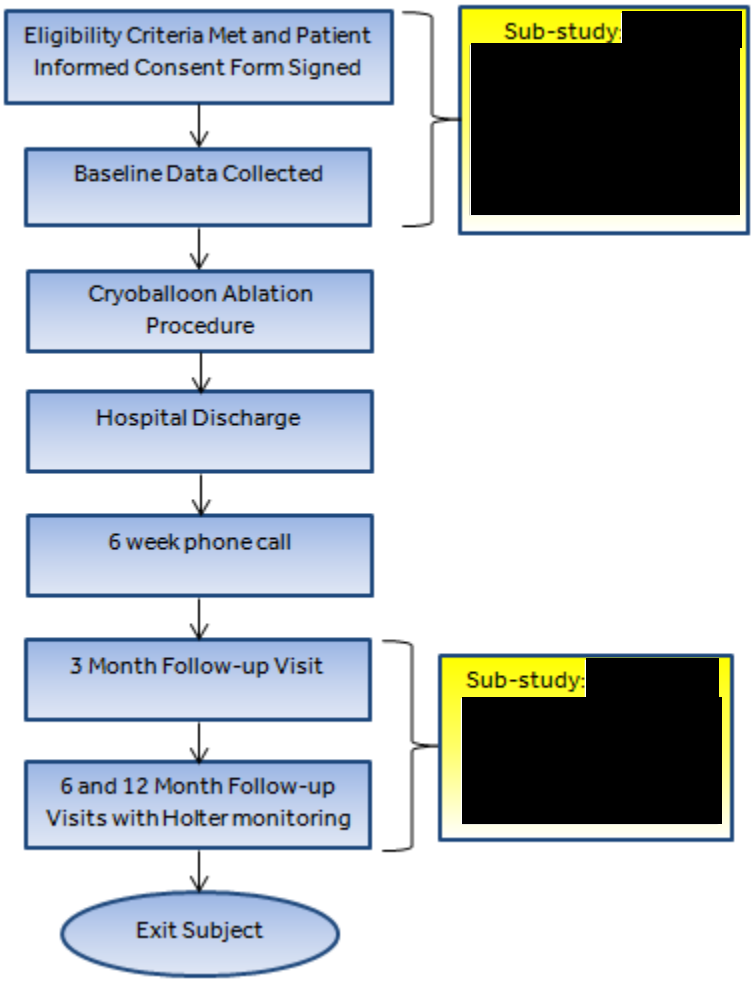
Medtronic, Inc. is sponsoring the STOP Persistent AF Study; a prospective, interventional, multi-center, non-randomized, single arm, unblinded clinical study. The study design diagram is shown in Figure 1.

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.

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.

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:

- 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.

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 NOTE 1: This definition includes events related to the investigational medical device or the comparator. NOTE 2: This definition includes events related to the procedures involved. NOTE 3: For users or other persons, this definition is restricted to events related to investigational medical devices. (ISO 14155:2011, 3.2)
Adverse Device Effect (ADE)	Adverse event related to the use of an investigational medical device NOTE 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. NOTE 2: This definition includes any event resulting from an error use or from intentional misuse of the investigational medical device. (ISO 14155:2011, 3.1)
Device Deficiency (DD)	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. NOTE: Device deficiencies include malfunctions, use errors and inadequate labeling (ISO 14155:2011, 3.15)
Relatedness	
Procedure related	An Adverse Event directly related to any portion of the procedure 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 a) led to death, b) led to serious deterioration in the health of the subject, that either resulted in: 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, or 3) in-patient or prolonged hospitalization (>24 hours), or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, c) led to fetal distress, fetal death or a congenital abnormality or birth defect NOTE 1: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event. (ISO 14155:2011, 3.37)
Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. (ISO 14155:2011, 3.36)
Unanticipated Adverse Device Effect (UADE)	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, an (investigational) device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the CIP or applicable (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. (21 CFR 812.3(s))
Unanticipated Serious Adverse Device Effect (USADE)	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report. NOTE: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report. (ISO 14155:2011 3.42)
Other	

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)* **Japan**: All serious, adverse events must be reported, whether or not there exists a

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

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

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.

[redacted]

[redacted]

[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.

<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)
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)
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)
Japan (investigational)</td><td rowspan="2">Medtronic, Inc.</td></tr>
<tr><td>239F5</td></tr>
<tr><td>209F3</td><td rowspan="3">Canada (non-investigational)
Europe (non-investigational)</td><td rowspan="3">Medtronic, Inc.</td></tr>
<tr><td>209F5</td></tr>
<tr><td>990063-020</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.
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.

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>
</table>

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) Europe (non-investigational)	Medtronic, Inc.
	209F5		
	990063-020		

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

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:

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.

<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.

	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) **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. **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. **Japan**: All SAEs classified as reportable events follow the applicable reporting requirements. (Pharmaceutical Affairs Law Enforcement Regulations, Article 273, 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) **Japan**: the Principal Investigator shall immediately report to the sponsor. (MHLW Ordinance 36, 2005, Article 68) **All other geographies:** Submit as soon as possible after the Investigator first learns of the event, and per local requirements

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%.

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.

18.3.3.2 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]

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.