VICTORY AF
Evaluation of Multielectrode Phased RF Technology in Persistent Atrial Fibrillation
Clinical Investigation Plan Version 6.0
21 NOV 2014
NCT01693120

Medtronic

Alleviating Pain · Restoring Health · Extending Life

VICTORY AF

Evaluation of Multiele**c**trode Phased **R**F Technolog**y** in Persistent **A**trial **F**ibrillation

Clinical Investigation Plan

Version 6.0

21 NOV 2014

IDE Number, G120067

Sponsors and Contacts
Medtronic, Inc. 8200 Coral Sea Street NE Mounds View, MN U.S.A. 55112 1-800-328-2518 And Medtronic International Trading Sarl Route du Molliau 31, 131 Tolochenaz Switzerland.

TABLE OF CONTENTS

[redacted]

LISTING OF TABLES

SPONSOR CONTACT INFORMATION

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

Table 1: Study sponsor contact information

Study sponsors and contacts
Worldwide Jennifer Lahr, Sr. Clinical Research Specialist 8200 Coral Sea St N.E. Mounds View, MN 55112 Direct Phone: 763.526.2781 Direct Fax: 763.367.1727 jen.lahr@medtronic.com *Europe* Alida Boi, Clinical Research Specialist Regional Clinical Centre Medtronic Clinical Research Institute Via Varesina, 162 20156 Milan, Italy Mobile [redacted] Fax: (+39 02) 24138204 alida.boi@medtronic.com

CROs AND CORE LABS

Table 2: CRO and core lab information

Contact Information	Duties performed
[redacted]	[redacted]
eImage Inc. *650 Sentry Parkway, Suite 1* *Blue Bell, PA 19422*	Responsible for reviewing pre-procedure and post-procedures visit CT scans for pulmonary vein stenosis. The core lab is responsible for identifying narrowing of pulmonary veins on post-procedural CT scans compared to the pre-procedural CT scan.
Cardiocore *One Preserve Parkway, Suite 600* *Rockville, MD 20852*	Responsible for reviewing 48 hour ambulatory ECG monitors for recurrent atrial fibrillation. The core lab will determine the total recording time and total analyzable time of the ambulatory ECG recording along with identifying the number of atrial fibrillation/atrial flutter episodes, the duration of each atrial fibrillation/atrial flutter episode and identification of other arrhythmias.

STEERING COMMITTEE

Table 3: Steering Committee contact information

Committee Member	Contact information
John Hummel, MD Coordinating Investigator	473 West 12th Ave, Suite 200 Columbus, OH 43210 Telephone: (614) 293-4967 Fax: (614) 247-7789 Email: john.hummel@osumc.edu Professional Position: Professor-Clinical, Cardiovascular Medicine
Hugh Calkins, MD	1800 Orleans Street Baltimore, MD 21287
Lucas Boersma, MD	Koekoekslaan 1 3435 CM Nieuwegein The Netherlands
Daryl Gress, MD	P.O. Box 800394 Hospital Drive West McKim Hall room 2027 Charlottesville, VA 22908
Atul Verma, MD	105-712 Davis Dr. Newmarket, Ontario L3Y 8C3 Canada
Lee Schwamm, MD	MGH, 55 Fruit Street Boston MA 02114

1. STUDY SUMMARY

1.1 Study Purpose

VICTORY AF is an IDE, prospective global, multi-center, single arm, investigational clinical study. The purpose of this clinical study is to evaluate the risk of procedure and/or device related strokes in subjects with persistent or long-standing persistent atrial fibrillation (AF) undergoing ablation with the Phased RF System.

1.2 Phased RF System Description

The Medtronic Phased RF System is intended to be used for mapping intracardiac electrograms and to deliver precise, temperature controlled radio frequency (RF) ablation therapy within the left atrium of the heart for the treatment of atrial fibrillation. The Phased RF System includes the GENius Multi Channel Radio Frequency Ablation Generator and three anatomically designed, multi-electrode catheters:

- Pulmonary Vein Ablation Catheter (PVAC) or Pulmonary Vein Ablation Catheter GOLD (PVAC GOLD)
- Multi-Array Septal Catheter (MASC)
- Multi-Array Ablation Catheter (MAAC)

1.3 Study Description

A maximum of 420 subjects will be enrolled in the study to ensure 300 subjects can be evaluated for the primary safety endpoint. Subjects will be followed for 6 months post index or reablation (if reablation required) procedure for the primary safety objective. The primary safety objective will be evaluated after at least 300 ablated subjects complete the 30 day post index or reablation procedure visit and have had the opportunity for a reablation procedure. The study may stop early for futility if more than 6 procedure and/or device related strokes occur within the 30 day peri-procedural period.

Study subjects from all geographies will be followed for 6 months following their final ablation procedure, or official study closure defined as when Medtronic and/or regulatory requirements have been satisfied per the Clinical Investigational Plan (CIP), whichever occurs first.

Expected total study duration is approximately 36 months, representing 24 months of enrollment and up to 12 months of subject follow-up.

1.4 Study Objectives

1.4.1 Primary Objective

Demonstrate that the observed incidence of procedure and/or device related incidence of new stroke (excludes transient ischemic attack) within 30 days of an ablation procedure (index or reablation) with the Phased RF System is less than 1.8% with observed upper confidence boundary that is less than 3.5%.

1.4.2 Secondary Study Objectives

- Characterize 6-month post-procedural effectiveness
- Characterize acute procedural success
- Characterize the incidence of PVS 3 months post ablation procedure as determined by MRI or CT scan
- [redacted]

1.5 Inclusion Criteria

1. History of symptomatic persistent or long-standing persistent atrial fibrillation defined as:
   - Persistent AF: sustained AF lasting > 7 days but no more than 1 year, or sustained AF lasting < 7 days but necessitating pharmacologic or electrical cardioversion; OR
   - Long-standing persistent AF: sustained AF lasting at least 1 year but no more than 4 years in duration.

     AND
   - Continuous AF as demonstrated on a 48-hour ambulatory ECG monitor at baseline AND
   - AF symptoms defined as the manifestation of:
     - Palpitations
     - Fatigue
     - Exertional dyspnea
     - Increased intolerance to routine activities (exercise intolerance)
2. Age 18-75 years
3. Failure of at least one class I or III anti-arrhythmic drug (AAD)

4. Willingness, ability and commitment to participate in baseline and follow-up evaluations for the full length of the study

1.6 Exclusion Criteria

1. Structural heart disease of clinical significance including:
   - Previous cardiac surgery (e.g. mitral valve repair) except CABG
   - NYHA Class III or IV CHF and/or documented ejection fraction <40% measured by acceptable cardiac testing (e.g. TEE)
   - Left atrial diameter of >55mm
   - 3+ mitral or aortic valvular heart disease
   - Stable/unstable angina or ongoing myocardial ischemia
   - Myocardial infarction (MI) within three months of enrollment
   - Congenital heart disease other than ASD or PFO without a right to left shunt where the underlying abnormality increases the risk of an ablative procedure
   - Prior ASD or PFO closure with a device using a percutaneous approach
   - Hypertrophic cardiomyopathy (LV septal wall thickness >1.5 cm)
   - Pulmonary hypertension (mean or systolic PA pressure >50mm Hg on Doppler echo)
2. Any prior ablation for atrial fibrillation in the left atrium
3. Enrollment in any other ongoing arrhythmia study protocol
4. Any ventricular tachyarrhythmia currently being treated where the arrhythmia or the management may interfere with this study
5. Active infection or sepsis
6. History of symptomatic cerebral vascular disease such as clinical stroke, TIA, or other diseases that manifest stroke-like symptoms (e.g. multiple sclerosis or seizure disorders)
7. Pregnancy or lactation
8. Untreatable allergy to contrast media
9. Any diagnosis of atrial fibrillation secondary to electrolyte imbalance, thyroid disease, or any other reversible or non-cardiovascular causes
10. Contraindicated for use of oral vitamin K antagonist (VKA e.g. warfarin) anticoagulation (e.g. history of blood clotting disorders)

11. Known sensitivities to heparin
12. Severe COPD (defined as an FEV_1 <1)
13. Severe co morbidity or poor general physical/mental health that, in the opinion of the Investigator, will not allow the subject to be a good study candidate (e.g. other disease processes like recent history of renal disease with GFR <30, recent history of cancer treatment, diminished mental capacity, substance abuse, shortened life expectancy , etc.)
14. Contraindicated to MRI
15. Any invasive cardiovascular procedure performed or planned within the 3 month periods before and/or after the ablation procedure

1.8 PVS Assessment Cohort

One hundred (100) subjects will be randomized to the PVS assessment cohort. The purpose of this sub-study is to characterize the incidence of pulmonary vein stenosis at three months post ablation.
This assessment will include CT/MRI scans prior to procedure and 3 months post procedure.

1.9 6 Month Post-procedural effectiveness

Success at 6 months is determined as:

- Acute procedural success, AND
- > 90% reduction in clinically significant AF/AFL by 48-hour ambulatory ECG monitor. Clinically significant AF/AFL is defined as; any AF/AFL episode lasting longer than 10 consecutive minutes in duration, AND
- Off amiodarone for at least 90 days and off all other class I and class III antiarrhythmic drugs for at least 60 days prior to the 6-month ambulatory ECG monitor, AND
- Free from DC cardioversion for AF for at least 60 days prior to the 6-month ambulatory ECG monitor

1.10 Acute procedural effectiveness

Acute procedural success will be defined as:

- Only Phased RF catheters used in the left atrium to achieve procedure success AND
- All targeted pulmonary veins were isolated (entrance block) AND

- CFAEs and high frequency intracardiac electrogram amplitudes were mapped and ablated as necessary with Phased RF catheters AND
- Sinus rhythm is restored at the end of the ablation procedure (with or without cardioversion)

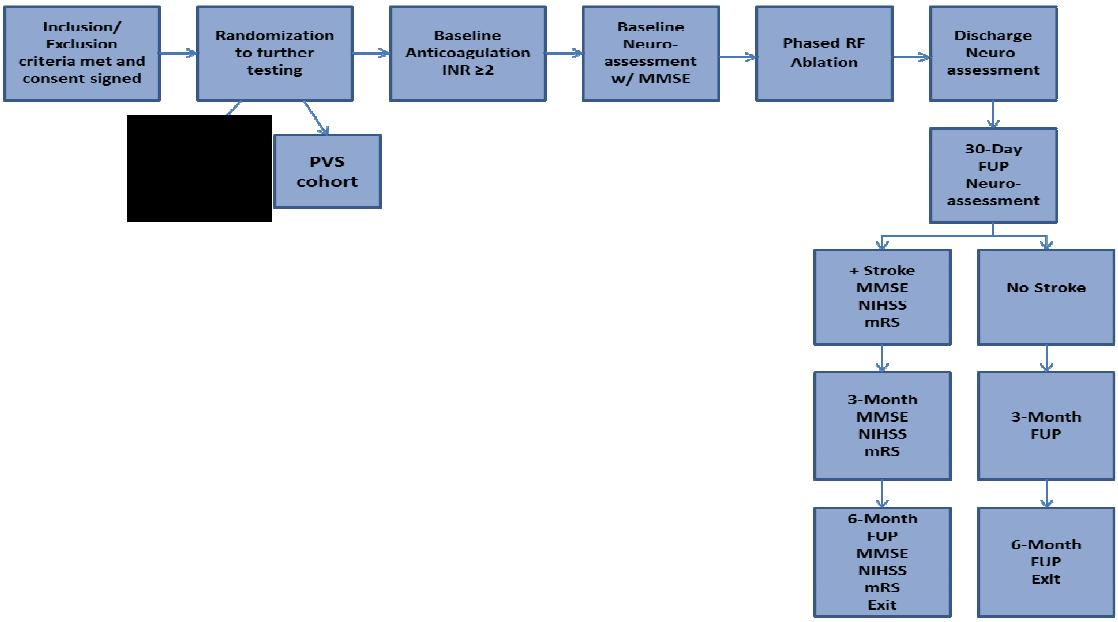
1.11 Sample Size

Up to 420 subjects with be enrolled to ensure that at least 300 subjects receive an index Phased RF ablation procedure and can be evaluated for the primary safety endpoint. Subject enrollment will stop once approximately 300 evaluable subjects are accrued.

1.12 Centers

The VICTORY AF study is expected to be conducted at up to 55 sites in Europe, Canada, and the United States (US).

1.13 Study Design



1.14 Anticoagulation Protocol

- Subjects must be on continuous vitamin K antagonist (VKA) (e.g. Warfarin/Coumadin) anticoagulation therapy throughout the VICTORY AF IDE study:
  - Baseline
    - On vitamin K antagonist (VKA) and two therapeutic INR readings within 30 days prior to index ablation procedure
  - Procedure
    - Continue therapeutic vitamin K antagonist anticoagulation
    - INR must be 2-3.5 on day of procedure

- Prior to transseptal puncture administer heparin bolus and start continuous heparin infusion to maintain ACT at or above 350 seconds
- Maintain continuous drip/flush of sheath when placed in left atrium
- Do not ablate with the Phased RF catheters unless ACT levels are at or above 350 seconds.
- Continue ACT measurements every 20-30 minutes thereafter until all Phased RF catheters are removed from body.

o Post-procedure

- Resume vitamin K antagonist (VKA) anticoagulation per subjects existing dose schedule
- Continue therapeutic vitamin K antagonist anticoagulation through end of study

2. INTRODUCTION

2.1 Study purpose

Medtronic, Inc. is sponsoring the E**v**aluation of Mult**i**ele**ct**rode Phased **R**F Technolog**y** in Persistent **A**trial **F**ibrillation (VICTORY AF) ablation study, prospective, unblinded, multi-center, investigational, global, clinical study. The purpose of this clinical study is to evaluate the risk of procedure and/or device related strokes in subjects with persistent or long-standing persistent atrial fibrillation (AF) undergoing ablation with the GENius Multi Channel Radio Frequency Ablation Generator, Pulmonary Vein Ablation Catheter (PVAC) or Pulmonary Vein Ablation Catheter GOLD (PVAC GOLD), the Multi-Array Septal Catheter (MASC), and the Multi-Array Ablation Catheter (MAAC) Catheter System.

2.2 Study description

The study is expected to be conducted at up to 55 centers located in Europe, Canada and the United States to support US Food and Drug Administration (FDA) marketing application. A maximum of 420 subjects will be enrolled in the study to ensure 300 subjects can be evaluated for the primary safety endpoint. Subjects will be followed for 30 days post reablation (if reablation required) procedure or 6 months post index procedure (if no reablation procedure required) for the primary safety objective. The primary safety objective will be evaluated after at least 300 ablated subjects complete the 30 day post index or reablation procedure visit and have had the opportunity for a reablation visit. Alternatively, the study may stop early for futility if more than 6 procedure and/or device related strokes occur within the 30 day peri-procedural period prior to completing enrollment.

Study subjects from all geographies will be followed for 6 months following their final ablation procedure, or official study closure defined as when Medtronic and/or regulatory requirements have been satisfied per the Clinical Investigational Plan (CIP), whichever occurs first. Accordingly, the expected total study duration is approximately 36 months, representing 24 months of enrollment and up to 12 months of subject follow-up.

3. BACKGROUND AND JUSTIFICATION

Atrial fibrillation is a debilitating disease with symptoms that reduce quality of life and put subjects at a higher risk of stroke than subjects with no atrial fibrillation. Current treatment options include antiarrhythmic drug therapy, catheter ablation for paroxysmal atrial fibrillation and concomitant surgical therapy. These treatment options have poor effectiveness outcomes and carry side effects from antiarrhythmic drugs and procedural risks from the surgical therapies. Currently in the U.S. catheter ablation is not indicated for the treatment of persistent and long standing persistent (herein referred to as persistent) atrial fibrillation and therefore subjects that have failed antiarrhythmic drug therapy and are not candidates or have failed surgical therapies have no other FDA approved treatment options.

Previous to this proposed study, the tailored treatment for permanent atrial fibrillation (TTOP-AF) study was conducted to demonstrate the safety and effectiveness the Phased RF system. TTOP-AF was conducted between 2007 and 2010 and presented to the FDA Circulatory System Devices Panel on October 27, 2011. Based on the TTOP-AF data the panel voted that the Phased RF system was effective in the treatment of subjects with persistent atrial fibrillation. However, the panel was concerned with the peri-procedural stroke rate and pulmonary vein stenosis rates. Therefore the panel voted that the benefits of the Phased RF system did not outweigh the risks of treating subjects with persistent atrial fibrillation. Thus, Medtronic with the agreement of the FDA is conducting this study to demonstrate that the Phased RF system is safe after the implementation of mitigation strategies to lower the peri-procedural stroke rate (i.e. anticoagulation and catheter programming requirements).

Therefore, the primary objective of the study is to confirm the safety of the Phased RF system and not to evaluate the system's effectiveness.

4. SYSTEM DESCRIPTION AND INTENDED USE

The Medtronic Phased RF System is intended to be used for mapping intracardiac electrograms and to deliver precise, temperature controlled radio frequency (RF) ablation therapy within the atria of the heart for the treatment of atrial fibrillation. The main components of the System are listed in Table 4.

Table 4: System component information

Model Number	Component	Investigational or Market-released (US, Canada)	Investigational or Market-released (Europe)
990018	GENius Multi-Channel RF Ablation Generator	Investigational (U.S. Only)	Market Released
990004	Catheter Interface Cable	Investigational (U.S. Only)	Market Released
990001	Multi-Array Septal Catheter (MASC)	Investigational (U.S. and Canada Only)	Market Released
990000	Multi-Array Ablation Catheter (MAAC)	Investigational (U.S. and Canada Only)	Market Released

Model Number	Component	Investigational or Market-released (US, Canada)	Investigational or Market-released (Europe)
990030	Pulmonary Vein Ablation Catheter (PVAC)	Investigational (U.S. Only)	Market Released
990078	Pulmonary Vein Ablation Catheter (PVAC GOLD)	Investigational (U.S. Only)	Market Released
990028	ECG Interface Box	Investigational (U.S. Only)	Market Released
990020	ECG Interface Box Cable	Investigational (U.S. Only)	Market Released
990027	ECG Amplifier Cable	Investigational (U.S. Only)	Market Released
990029	GENius Jr. Remote Control	Investigational (U.S. Only)	Market Released
990041, 990042	Remote Control Cable 15 or 25ft	Investigational (U.S. Only)	Market Released
990025	Power Cord, North America	Investigational (U.S. Only)	N/A*
990024	Power Cord, UK	N/A*	Market Released (UK Only)
990023	Power Cord, Continental EU	N/A*	Market Released (Continental EU)

* Not applicable since Power Cords for specific regions will not be included in locations where they are not used.

[redacted]

[redacted]

The System supports delivery of RF energy to all catheters listed in the Table above. The System has the ability to detect which catheter is connected and set appropriate system parameters. All cardiac catheters are provided sterile and labeled for single use only.

In the U.S., the Phased RF system will be labeled as investigational use only. In Canada, the MASC and MAAC catheters will be labeled as investigational use only. For Europe, the Phased RF system will be labeled as market released.

[redacted] Ablation duration is adjustable from 45 to 120 seconds in 5 second increments. The system includes a safety STOP switch to immediately terminate ablation energy if required during the clinical procedure.

The System will withstand a 5KvDC defibrillator pulse without loss of patient safety and/or function. The system has been designed to meet the requirements for Class 1 Type CF Medical Electrical Equipment. Instructions for use of the devices used in this study are provided in their respective manuals.

4.1 Additional system components

Currently approved patient return electrodes, transseptal sheaths, dilators and needles will be used during the Phased RF ablation procedure. These components are not considered investigational and will not be tracked on the device tracking logs.

4.2 Labeling

Since the devices used in the VICTORY AF study are market-released in Europe, original labeling will be used unless local regulations require otherwise. Labeling of CE-marked devices will follow local language requirements.

In Canada, Investigational products labeled as required under Subsections 86(c) and 86(d) of the Medical Devices Regulations.

5. REGULATORY COMPLIANCE

The VICTORY AF clinical study is an Investigational Device Exemption (IDE) study in the United States.

The VICTORY AF clinical study is designed to reflect good clinical practice principles. These include the protection of the rights, safety and well-being of human subjects, controls to ensure the scientific conduct, credibility and data integrity of the clinical investigation, and the definition of responsibilities of the sponsor and investigators.

The study will be conducted according to the Declaration of Helsinki, this Clinical Investigation Plan (CIP) and federal, national and local laws, regulations, standards, and requirements of the countries/geographies where the study is being conducted. The principles of the Declaration of Helsinki are implemented in this study by means of the Patient Informed Consent (IC) process, Institutional Review Board (IRB) or Medical Ethics Committee (MEC) approval, study training, clinical trial registration, pre-clinical testing, risk benefit assessment, publication policy, etc.

In the United States, this study will be conducted in compliance with relevant local laws which are US FDA 21 CFR parts

- 11: Electronic Records; Electronic Signatures
- 50: Protection of Human Subjects
- 54: Financial Disclosure by Clinical Investigators
- 56: Institutional Review Boards
- 812: Investigational Device Exemptions

The Phased RF System is approved for use in the EEA (European Economic Area). The study will be conducted in accordance with local law and the transposition of the applicable requirements of the Medical Device Directive in local law. In regions where the system is market released, the system will be used in the manner for which it was intended and therefore in Europe the VICTORY AF clinical study is a post market study.

In Canada, the study will be conducted in accordance with Canada Medical Device Regulations, SOR/98-282; 77, 59, Mandatory Problem Reporting 59(1), 59(2), 60 (1))

This 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/.

In addition to following the governing regulations noted above, any additional requirements of the individual study center's IRB/MEC or regulatory authority will also be followed by the study center where applicable.

Approval of the CIP or CIP amendments is required from the following groups prior to any study procedures at a study center: Medtronic, geography-specific regulatory authorities (if regulatory approval is required) and an independent medical ethics committee or institutional review board.

6. METHODOLOGY

6.1 Study design

This study is a prospective, unblinded, multi-center, investigational (U.S. and Canada), global, clinical study designed to evaluate the procedure and/or device related stroke rate within 30 days after an ablation procedure with the Medtronic Phased RF System. In regions where the system is market released, the system will be used in the manner for which it was intended. The primary safety objective will be evaluated after at least 300 ablated subjects complete the 30 day post index or reablation procedure visit and have had the opportunity for a reablation visit. The study may stop early for futility if more than six (6) procedure and/or device related strokes occur prior to completing enrollment.

6.2 Study objectives

6.2.1 Primary safety objective

Demonstrate that the observed incidence of procedure and/or device related incidence of new stroke (excludes transient ischemic attack) within 30 days of an ablation procedure (index or reablation) with the Phased RF System is less than 1.8% with observed upper confidence boundary that is less than 3.5%.

The definition of stroke is provided in the Table below. To meet the primary endpoint an event must meet all of the criteria in Table 5 below as determined by the clinical events committee (CEC).

Table 5: Protocol defined stroke

Definition	Hemorrhagic and Ischemic stroke with rapid onset of a focal or global neurological deficit or other neurological signs/symptoms consistent with stroke

Symptom duration	Duration of focal or global neurological deficit ≥24 hours; **OR**
	Duration of focal of global neurological deficit <24 hours **IF:**
	• Therapeutic interventions
	  ○ Thrombolytic therapy
	  ○ Intracranial angioplasty
	OR
	• Neuroimaging documents a new hemorrhage or ischemic infarct **OR**
	• Neurological deficit results in death

Periprocedural definition	Within 30 days of Phased RF ablation procedure where the investigational catheter was placed in the left atrium
Diagnosis	Appropriate diagnostics will be determined by the site's neurologist's clinical evaluation and include one or more of the following: • Clinical signs and symptoms consistent with focal or global neurologic deficit • Neuroimaging procedure (CT or MR scan or cerebral angiography) • Lumbar puncture (i.e. subarachnoid hemorrhage) **AND** Adjudicated as peri-procedural stroke by clinical events committee

[redacted]

6.2.2 Secondary effectiveness objectives

6.2.2.1 6-Month Post-Procedural Effectiveness

Characterize the 6-month post-procedural effectiveness.

6-Month effectiveness will be defined as:

- Acute procedural success, AND
- ≥ 90% reduction in clinically significant AF/AFL by 48-hour ambulatory ECG monitor. Clinically significant AF/AFL is defined as; any AF/AFL episode lasting longer than 10 consecutive minutes in duration, AND
- Off amiodarone for at least 90 days and off all other class I and class III antiarrhythmic drugs for at least 60 days prior to the 6-month ambulatory ECG monitor, AND
- Free from DC cardioversion for AF for at least 60 days prior to the 6-month ambulatory ECG monitor

Only those subjects that have completed both a baseline and 6-month 48 hour ambulatory ECG monitor or are 6-month effectiveness failures based on other criteria will be included in the PMA effectiveness analysis cohort. Two ablation procedures with the Phased RF system are allowed to achieve procedural effectiveness.

6.2.2.2 Acute procedure success

Characterize acute procedural effectiveness.

Acute procedural success will be defined as:

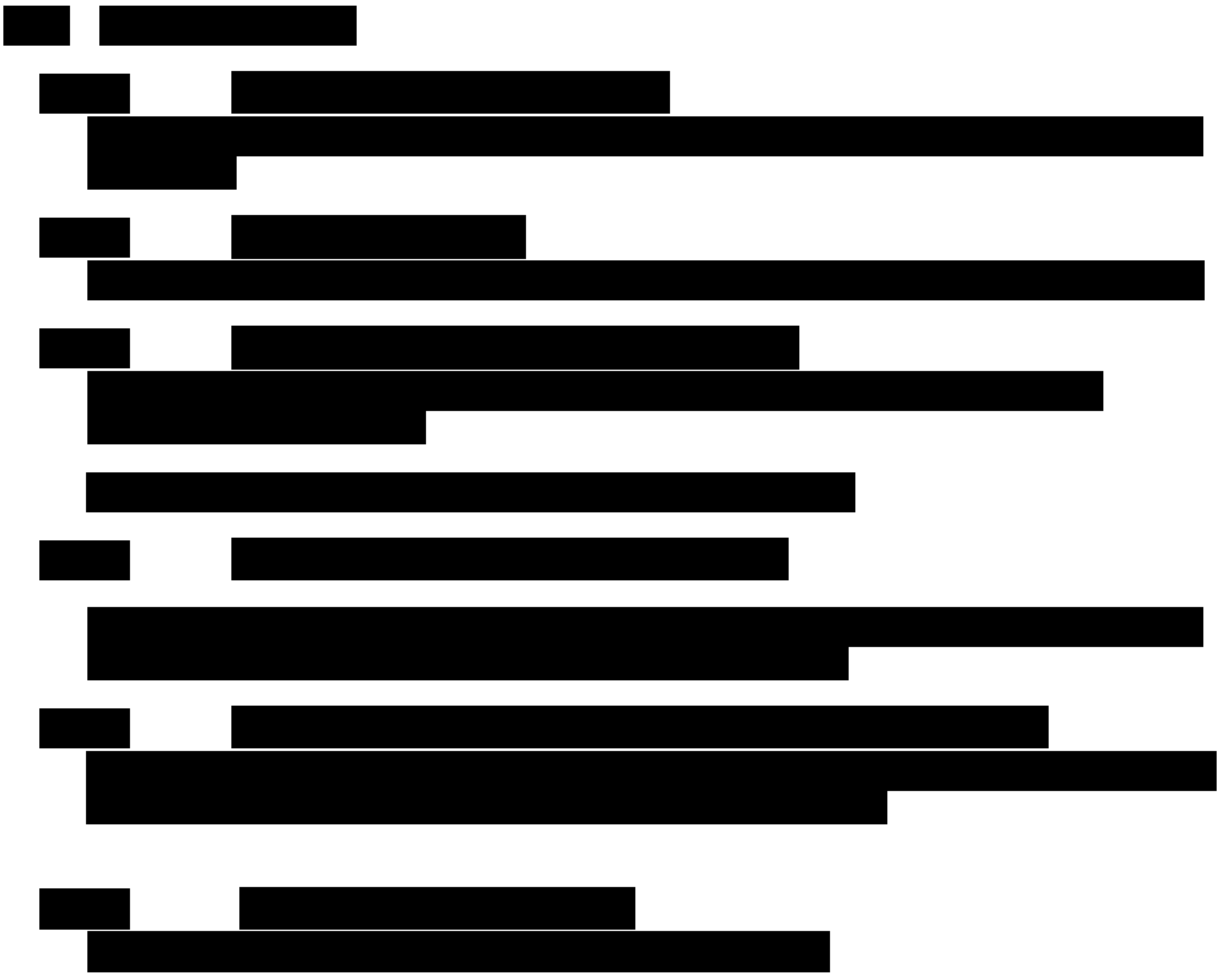
- Only Phased RF catheters used in the left atrium to achieve procedure success AND
- All targeted pulmonary veins were isolated (entrance block) AND
- CFAEs and high frequency intracardiac electrogram amplitudes were mapped and ablated as necessary with Phased RF catheters AND
- Sinus rhythm is restored at the end of the ablation procedure (with or without cardioversion)

6.2.3 Secondary safety objective

6.2.3.1 Pulmonary vein stenosis (PVS)

Characterize the incidence of PVS 3 months post ablation procedure as determined by MRI or CT scan.

This objective will be evaluated in a subset of 100 subjects.



6.3 Subject selection criteria

Subjects will be screened to ensure they meet all of the inclusion and none of the exclusion criteria. Institutional Review Board / Medical Ethics Committee (IRB/MEC) approval of the VICTORY AF Clinical Investigation Plan and Informed Consent Form must be obtained prior to enrolling patients in the study.

6.3.1 Inclusion criteria

1. History of symptomatic persistent or long-standing persistent atrial fibrillation defined as:
   - Persistent AF: sustained AF lasting > 7 days but no more than 1 year, or sustained AF lasting < 7 days but necessitating pharmacologic or electrical cardioversion; OR
   - Long-standing persistent AF: sustained AF lasting at least 1 year but no more than 4 years in duration.

     AND
   - Continuous AF as demonstrated on a 48-hour ambulatory ECG monitor at baseline AND
   - AF symptoms defined as the manifestation of:
     - Palpitations
     - Fatigue
     - Exertional dyspnea
     - Increased intolerance to routine activities (exercise intolerance)
2. Age 18-75 years
3. Failure of at least one class I or III anti-arrhythmic drug (AAD)
4. Willingness, ability and commitment to participate in baseline and follow-up evaluations for the full length of the study

6.3.2 Exclusion criteria

1. Structural heart disease of clinical significance including:
   - Previous cardiac surgery (e.g. mitral valve repair) except CABG
   - NYHA Class III or IV CHF and/or documented ejection fraction <40% measured by acceptable cardiac testing (e.g. TEE)
   - Left atrial diameter of >55mm
   - 3+ mitral or aortic valvular heart disease
   - Stable/unstable angina or ongoing myocardial ischemia
   - Myocardial infarction (MI) within three months of enrollment
   - Congenital heart disease other than ASD or PFO without a right to left shunt where the underlying abnormality increases the risk of an ablative procedure
   - Prior ASD or PFO closure with a device using a percutaneous approach
   - Hypertrophic cardiomyopathy (LV septal wall thickness >1.5 cm)

- Pulmonary hypertension (mean or systolic PA pressure >50mm Hg on Doppler echo)

2. Any prior ablation for atrial fibrillation in the left atrium
3. Enrollment in any other ongoing arrhythmia study protocol
4. Any ventricular tachyarrhythmia currently being treated where the arrhythmia or the management may interfere with this study
5. Active infection or sepsis
6. History of symptomatic cerebral vascular disease such as clinical stroke, TIA or other diseases that manifest stroke-like symptoms (e.g. multiple sclerosis or seizure disorders)
7. Pregnancy or lactation
8. Untreatable allergy to contrast media
9. Any diagnosis of atrial fibrillation secondary to electrolyte imbalance, thyroid disease, or any other reversible or non-cardiovascular causes
10. Contraindicated for use of oral VKA (e.g. warfarin) anticoagulation (e.g. history of blood clotting disorders)
11. Known sensitivities to heparin
12. Severe COPD (defined as an FEV_1 <1)
13. Severe co morbidity or poor general physical/mental health that, in the opinion of the Investigator, will not allow the subject to be a good study candidate (e.g. other disease processes like recent history of renal disease with GFR <30, recent history of cancer treatment, diminished mental capacity, substance abuse, shortened life expectancy, etc.)
14. Contraindicated to MRI
15. Any invasive cardiovascular procedure performed or planned within the 3 month periods before and/or after the ablation procedure

6.4 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.
- Subjects will be selected randomly (excluding the first enrolled subject at each center) for evaluating the incidence of [redacted] pulmonary vein stenosis.
- Demographics and medical history will be collected at baseline in order to later assess possible characteristics that may influence study endpoints.

- Data collection requirements and study procedures will be standardized across all study centers.
- No more than 15% (45) of ablated study subjects may come from a single center.
- No more than 33% (100) of ablated study subjects may come from geographies outside the US.
- All study center and Medtronic personnel will be trained using standardized training materials.
- All study clinicians will be trained on and required to follow the Clinical Investigation Plan.
- All study investigators will be required to meet the requirements of 21 CFR Part 54, Financial Disclosure by Clinical Investigators.
- Regular monitoring visits will be conducted to verify source data and adherence to the Clinical Investigation Plan and source data.
- A core laboratory will be used to characterize [redacted] all baseline and 6-month follow-up 48-hour ambulatory ECG monitors
- [redacted]
- A core laboratory will be used to evaluate CT or MRI images for pulmonary vein stenosis at baseline and at the 3-month post-procedure follow-up visit.
- An independent clinical events committee (CEC) will be utilized to regularly review and adjudicate reported adverse events.
- An independent data monitoring committee (DMC) will be utilized to review accumulating safety data, help safeguard the interests of study subjects, and monitor the overall conduct of the study

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

6.5 Subset Selection Randomization Process

Upon confirmation that all inclusion and no exclusion criteria have been met, the Patient Informed Consent has been signed, and baseline testing has been completed, a subject may be randomized using an electronic randomization system to [redacted] the PVS assessment cohort. It is recommended that randomization occur as close as possible but prior to the index Phased RF procedure to minimize study attrition following randomization.

Specifically, 100 subjects will be randomly selected from the first 200 enrolled subjects to participate in the PVS assessment cohort. The randomization schedule will not allow the first enrolled subject at a study center to be selected into the PVS assessment cohort.

[redacted]

The remaining subjects not randomly selected for participation in the PVS assessment cohort [redacted] will have no additional assessments performed.

A Medtronic statistician will create the randomization schedules and the randomization schedule will ensure that subjects cannot be randomized to [redacted] PVS assessment cohorts.

7. STUDY PROCEDURES

Center personnel training will be completed prior to participation in this clinical study. 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 specific activities. Study materials will be provided to center staff prior to site initiation. The site neurologist must be certified in administering the National Institute of Health Stroke Scale (NIHSS) and the Modified Rankin Score (mRS). The site radiology staff (e.g. technicians) may be trained to the study required imaging parameters.

Medtronic personnel may provide technical support, including completion of a technical support sheet, during the ablation procedure.

7.1 Investigation sites

Sites must have an EP physician experienced in ablation of atrial fibrillation and trained by Medtronic personnel in the handling of the Phased RF System. Sites are also required to have a Neurologist (or equivalent physician with specialization in stroke diagnosis and treatment, e.g. British Association of Stroke Physicians (BASP) in the UK) and adequate infrastructure and diagnostics to comply with study required procedures.

A list of participating investigators and investigational sites will be submitted under a separate cover.

7.2 Site activation

During the activation process (prior to subject enrollment), Medtronic will train site personnel on the clinical investigation plan, relevant standards and regulations, informed consent, written clinical investigation agreements and on data collection and reporting tools. If new members join the investigational site team, they will receive training on the applicable clinical investigation requirements relevant to their role before contributing to the clinical investigation. Additionally, Medtronic will emphasize the importance of enrolling women in this study during the site training process. Medtronic will also work

with the sites to develop strategies to improve the participation of women in this study that may include, but are not limited to: tailored communication strategies, inclusion of health care practitioners to help with recruitment, monetary incentives, flexibility of follow up schedule, and reviewing screening logs to identify trends that are inhibiting enrollment of women.

Prior to performing study related activities, all local regulatory requirements shall be fulfilled, including, but not limited to the following: IRB/MEC approval of the current version of the CIP and Patient Informed Consent form, regulatory authority approval or notification as required per local law, fully executed Clinical Trial Agreement (CTA), Financial Disclosure, investigator Curriculum Vitae (CV), Delegated Task List (DTL) and documentation of study training. In addition, all participating site 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 written documentation of study center/investigator readiness, this letter must be received prior to subject enrollment.

7.3 Equipment requirements

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

- E7506 Valley lab patient return electrodes (2 per subject ablation)
- MRI system [redacted]
- CT scanner
- ACT analyzer capable of providing measurements every 10 minutes*

*NOTE: ACT analyzer calibration records must be made available for sponsor review prior to each Phased RF ablation procedure.

7.4 Patient informed consent process

Patient informed consent is defined as legally effective, documented confirmation of a subject's (or their legally authorized representative or guardian) voluntary agreement to participate in a particular clinical 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 Consent and a/an Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language as required by law that has been approved by Competent Authorities (CA), the investigational center's Medical Ethics Committee (MEC), Institutional Review Board (IRB), or Head of Medical Institution and signed and dated by the subject (or their legally authorized representative or guardian). 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.

Prior to enrolling subjects, each investigational center's MEC, IRB, or Head of Medical Institution will be required to approve the Consent Form (CF), and Authorization to Use

and Disclose Personal Health Information/Research Authorization/other privacy language as required by law. The document(s) must be controlled (i.e. versioned and/or dated) to ensure it is clear which version(s) were approved by the (MEC) or (IRB), or Head of Medical Institution. Any adaptation of the sample Consent Form must be reviewed by Medtronic and the MEC or IRB, or Head of Medical Institution reviewing the application prior to enrolling subjects.

Prior to initiation of any study-specific procedures, patient informed consent must be obtained from the subject (or their legally authorized representative or guardian). Likewise, privacy or health information protection regulation in other geographies may require subjects to sign additional forms to authorize centers to submit subject information to the study sponsor. The Consent Form and 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 or guardian) in a language he/she is able to read and understand. The process of patient informed consent must not be conducted using coercion or undue improper influence on or inducement of the subject to participate by the investigator or other center personnel.

The process of obtaining patient informed consent shall:

- Not waive or appear to waive subject's legal rights
- Use language that is non-technical and understandable to the subject
- Provide ample time for the subject to read and understand the informed consent form and to ask questions, receive answers and consider participation
- Include a personally dated signature of the subject acknowledging that their participation in the study is voluntary
- EEA only: Include a personally dated signature by the principal investigator or authorized designee responsible for conducting the informed consent process

If the Consent Form 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 a Legally Authorized Representative or guardian is utilized, copy of this legal delegation must be retained in the subject's records. In the event the subject cannot read and/or write, witnessed (impartial third party) patient informed consent will be allowed, provided detailed documentation of the process is recorded in the subject's case history and the witness signs and dates the patient informed consent. The subject should "make his mark" (sign or otherwise physically mark the document so as to indicate consent) on the ICF as well. The Consent 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 or a copy of the signed Consent Form must be filed in the hospital/clinical chart and with the subject's study documents. A copy of the *signed and dated* Consent

Form and signed Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language as required by law must be provided to the subject.

The Consent Form and Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language as required by law must be available for monitoring and auditing.

Any changes to a previously approved Informed Consent Form throughout the course of the study must be approved by the MEC or IRB, or Head of Medical Institution reviewing the application before being used to consent a prospective study subject. The MEC or IRB, or Head of Medical Institution –approved Consent Form must also be submitted to Medtronic for review and approval. The document(s) must be controlled (i.e. versioned and/or dated) to ensure it is clear which version(s) were approved by the Medical Ethics Committee (MEC) or Institutional Review Board (IRB), or Head of Medical Institution. All important new information should be provided to new and existing subjects throughout the study. For existing subjects, the informed consent process as described above needs to be repeated for significant changes as determined by the MEC, IRB or Head of Medical Institution.

7.5 Data collection

Clinical data is collected at designated time points throughout the study. Data will be collected using an electronic data management system for clinical studies. 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 study centers for resolution. Study management reports may be generated by Medtronic to monitor data quality and study progress. At the end of the study, the data will be frozen and retained indefinitely by Medtronic. Data collection requirements are summarized in Table 6 below.

Table 6: Data collection and study procedure requirements at subject visits

		Ablation Procedure			Repeat Ablation Procedure (1-180 days)							
	Baseline	Procedure	Post-procedure	Discharge	Baseline	Procedure	Post-procedure	Discharge	30 day	3 month	6 month	Unscheduled
Consent	X											
Incl/Excl Criteria	X											
History	X											
Physical exam	X(11)			X	X			X	X	X	X	X
Pregnancy Screen (if applicable per local requirement)	X											
Standard neurologic evaluation (performed by neurologist)	X			X	X			X	X	X(10)	X(10)	X
Concomitant medications	X		X	X	X			X	X	X	X	X
Arrhythmic Sx review	X				X				X	X	X	X
12 lead ECG	X(11)			X	X			X	X	X	X	X
Cardioversion log	X				X				X	X	X	X
TTE	X(2)				X(2)							
Esophageal visualization		X				X						
MRI or CT for PVS	X(3, 11)									X(3)		
[redacted]		[redacted]		[redacted]					[redacted]			
NIHSS (performed by neurologist)				X(1)				X(1)	X(1)	X(1)	X(1)	X(1)
MMSE (performed by neurologist)	X			X(1)				X(1)	X([redacted])	X([redacted])	X(1)	X(1)
mRS (performed by neurologist)				X(1)				X(1)	X(1)	X(1)	X(1)	X(1)
INR	X	X	X	X	X	X	X	X	X	X	X	X
ACT		X				X						
48 hour ambulatory ECG monitoring	X(11)										X	
TEE		X(5)				X(5)						
AE review		X	X	X	X	X	X	X	X	X	X	X
GENius Data File Collection		X				X						

1. Only for subjects diagnosed with protocol defined stroke
2. Not required for repeat ablation procedures as long as last TTE was performed within 6 months of reablation procedure
3. Only required for the subset subjects in the PVS assessment cohort. The same technology should be used for baseline and 3 month scans

[redacted]

5. Required 48 hours prior to ablation procedure

[redacted]

10. Only for subjects that have been diagnosed with a focal or global neurological deficit and/or signs/symptoms suggestive of stroke
11. Must be completed within 3 months prior to index ablation procedure

7.6 Subject visit schedule

After receiving notice of ablation procedure, Medtronic will provide the target dates and windows for each visit to the investigational center and if subject is to be included in the [redacted] PVS subset. Should a subject 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 late follow-up visits. Therefore, a late visit is preferred over a missed visit, but must be accompanied by a deviation.

The follow-up schedule will be reset for subjects that require a reablation procedure with the Phased RF system. For example, if subjects had reablation procedures after their 30-day follow-up visits, new target dates will be generated for their new 30-day follow-up visits and revised target dates for their 3-month and 6-month post-ablation visits.

Table 7: Visit Windows

Study Follow-up Visit	Window (Calculated calendar days post-ablation from the subjects last ablation procedure)		
	Window Start (days post-procedure)	Target (days post-procedure)	Window End (days post-procedure)
Procedure	0	0	0
Discharge	1	1	7*
30 Day	30	30	37
3 Month	76	90	104
6 Month	180	180	210**

[redacted].

**6-month ambulatory ECG monitoring must occur within the 6-month visit window. Subjects discontinuing Amiodarone at the 3-month visit should not start their 6-month ambulatory ECG monitor until at least 90 days following Amiodarone discontinuation.

7.7 Study procedure details

Physical Exam: Conduct a complete physical exam including but not limited to height, weight, arrhythmic history and cardiovascular history. For index Baseline visit, the exam should be completed within the 3 months prior to the ablation procedure.

Pregnancy Screen: If the subject is a female of child-bearing potential, a serum or urine pregnancy test must be performed. If not of child-bearing potential, make sure there is documentation in subject's medical record to indicate this.

Neurologic Evaluation: The site neurologist will conduct a standard neurologic exam on all subjects to determine if focal or global neurological deficit or other neurological signs/symptoms consistent with stroke are present at the time of the study visit.

The Baseline neurologic evaluation may be completed within the 2 weeks prior to the index ablation procedure.

Upon the sites' awareness of Unscheduled visits, the neurologic evaluation conducted by the site neurologist should be completed as soon as possible.

National Institute of Health Stroke Scale (NIHSS): The site neurologist will administer the NIHSS to subjects that have been identified to have focal or global neurological deficit or other neurological signs/symptoms consistent with stroke at the time the deficit or symptoms present and all subsequent study follow up visits.

Mini-Mental State Exam (MMSE): The site neurologist will administer the MMSE to all subjects at the baseline visit.

In addition, the site neurologist will administer the MMSE for the following:

- [redacted]
- Subjects that have been identified to have post-ablation focal or global neurological deficit (or other neurological signs/symptoms consistent with stroke) at the time the deficit or symptoms present and all subsequent study follow up visits.

Modified Rankin Score (mRS): The site neurologist will administer the mRS to subjects that have been identified to have focal or global neurological deficit (or other

neurological signs/symptoms consistent with stroke) at the time the deficit or symptoms present and all subsequent study follow up visits.

Concomitant Medications: All prescribed cardiovascular and vitamin K antagonist medications and dosages will be collected at protocol defined study visits and unscheduled study visits.

For purposes of the study, cardiovascular medications are defined as the following major types of cardiovascular medications per American Heart Association (AHA):

- Anticoagulants
- Antiplatelet agents
- Angiotensin-converting enzyme (ACE) inhibitors
- Angiotensin-II receptor blockers (or inhibitors), also known as ARBs
- Antiarrhythmic drugs (AADs)
- Beta blockers
- Calcium channel blockers
- Diuretics
- Vasodilators
- Digitalis preparations
- Statins

Therapeutic anticoagulation: Therapeutic anticoagulation is defined as an INR of 2.0 to 3.5. All subjects are required to be prescribed to a vitamin K antagonist (VKA) 30 days prior to the ablation procedure to achieve therapeutic anticoagulation. Subjects will then be required to stay on a VKA for the remainder of their study participation.

Antiarrhythmic Drug (Class I and III) and Direct Cardioversion Use: All subjects will be allowed to be prescribed to one or more class I and/or III antiarrhythmic drug and undergo direct cardioversion as described in Table 8 below.

Table 8: Class I and III Antiarrhythmic Drug Use Intervals

AAD & DC Cardioversion	Use Intervals	
Amiodarone	Allowed; Baseline to 3 month visit	Not allowed within 90 days prior to 6-month Holter *
Class I and III AADs	Allowed; Baseline – 4 months	Not allowed within 60 days prior to 6-month Holter*
DC cardioversions	Allowed; Baseline – 4 months	Not allowed within 60 days prior to 6-month Holter*

*For patient safety and welfare, investigators are allowed to prescribe the use of AAD or DC Cardioversions if medically necessary during “not allowed” use intervals. However, this will be considered a protocol deviation.

History of Atrial Fibrillation: At the time of enrollment, the investigators are required to indicate in the subjects' medical record whether the existing atrial fibrillation is persistent or long-standing persistent as defined in the inclusion criteria. In addition, the subject will be required to complete a 48-hour ambulatory ECG monitor at the baseline visit to demonstrate persistent AF at the time of enrollment.

Arrhythmic symptom review: Subjects will be queried to determine what symptoms if any, they are experiencing due to atrial fibrillation at protocol defined clinic visits and unscheduled clinic visits.

12 Lead ECG: Will be collected at protocol defined study visits and unscheduled study visits to determine heart rhythm along with specific intervals. The Baseline 12 lead ECG should be completed within the 3 months prior to the index ablation procedure.

Cardioversion Log: At protocol defined study visits and unscheduled study visits the cardioversion log will be updated with the date of any electrical cardioversions that have been performed since last clinic visit.

48-hour ambulatory ECG monitor: Will be collected at protocol defined study visits to determine heart rhythm. Examples of ambulatory ECG monitors are Holter monitors, wearable wireless adhesive ECG monitors (e.g. ECG patch monitors).

For the Baseline ambulatory ECG monitoring, this should be completed within the 3 months prior to the index ablation procedure to document study subject has continuous AF. Subjects may be asked to repeat an ambulatory ECG monitoring session if less than 24 hours of analyzable monitoring time is obtained or continuous AF is not demonstrated. The ambulatory ECG monitoring technology used at the 6-month visit should be the same as the technology used at the baseline visit.

Trans-thoracic echocardiogram (TTE): Will be collected at Baseline or within previous 6 months of the index or reablation procedure to determine atrial volume and size.

Trans-esophageal echocardiogram (TEE): Will be collected within 48 hours prior to the index or reablation procedure to rule-out left atrial thrombus.

If a left atrial thrombus is visualized during pre-procedure TEE, the study subject will not undergo the study ablation procedure at that time.

MRI/CT scan (Chest): Will be done prior to ablation procedure and 3 months post index ablation procedure for the assessment of PVS in subjects in the PVS assessment cohort.

For the Baseline scan, this should be completed within the 3 months prior to the index ablation procedure.

The imaging technology (MRI, CT) used at Baseline pre-procedure scan must match the 3-Month post-procedure scan technology for a given study subject.

[redacted]

International normalized ratio (INR): Blood will be drawn at each study visit (i.e. within the study visit window) to determine the subject's INR.

Two (2) INR levels demonstrating the study subject is therapeutic on VKA are required in the 30 days prior to the index ablation procedure. INR draws from other health care providers are permitted.

Esophagus visualization: Perform visualization prior to ablation procedure using site standard procedure.

7.8 Enrollment and Baseline

When a patient signs and dates the Consent Form, he/she is considered a subject enrolled in the study. The date the subject signed the Consent Form and data protection authorization must be documented. The following information is required to be collected at the Baseline visit:

- Medical history
- Pregnancy screen (if applicable)
- Physical exam
- 12 lead ECG (within 3 months of index ablation procedure)
- 48 hour ambulatory ECG monitor (within 3 months of index ablation procedure)
- Review of arrhythmic symptoms
- Review of antiarrhythmic drug use
- Neurologic evaluation
- MMSE
- Concomitant medication
- Cardioversion history
- Anticoagulation status; subjects are required to be prescribed to a vitamin K antagonist (VKA) 30 days prior to the ablation procedure.
  - Two therapeutic INR readings (≥2.0) within 30 days prior to the ablation procedure
- TTE (within 6 months of ablation procedure to determine LA size, LVEF, LV wall thickness)

- Randomize subject to [redacted] PVS assessment cohorts. Note that not all subjects may be selected for additional [redacted] PVS screening.

7.9 Phased RF Ablation Procedure

7.9.1 Pre-procedure evaluation

The following information is required to be collected at the ablation procedure or within specified timeframe prior to the ablation procedure:

- [redacted]
- Spiral CT or MRI of pulmonary veins for subjects randomized to PVS surveillance assessment cohort (Chest) (within 3 months prior to procedure). Spiral CT or MRI of pulmonary veins for subjects randomized to the PVS assessment cohort are only required for the index ablation procedure.
- Concomitant medications
- TEE to rule out left atrial thrombus (within 48 hours prior to procedure). If a left atrial thrombus is visualized during pre-procedure TEE, the study subject will not proceed to the study ablation procedure at that time.
- Visualize the esophagus prior to ablation
- INR (required to be 2.0 to 3.5 on the day of procedure)

NOTE: Other cardiac rhythm abnormalities requiring treatment in the right atrium may be detected during the Phased RF ablation procedure. When necessary for subject welfare, other approved ablation catheters may be utilized at the Investigator's discretion. Investigators are allowed to ablate arrhythmic triggers originating from the superior vena cava (SVC) and/or the cavotricuspid isthmus using indicated ablation catheter. Specifically, cavotricuspid isthmus ablation will be allowed providing one of the following criteria is satisfied:

- History of typical atrial flutter OR
- Inducible cavotricuspid isthmus dependent atrial flutter

The PVAC or PVAC GOLD catheter may be used to ablate within the SVC. All ablations will be documented on the ablation procedure CRF.

7.9.2 Procedure preparation

- Prior to transseptal puncture administer heparin bolus and start continuous heparin infusion to maintain ACT at or above 350 seconds
- Maintain continuous drip/flush of sheath when placed in left atrium
- Do not ablate with the Phased RF catheter unless ACT levels are at or above 350 seconds.

- Continue ACT measurements every 20-30 minutes thereafter until all Phased RF catheters are removed from body

7.9.3 PVAC or PVAC GOLD catheter introduction

- Pause continuous drip/flush of left atrial sheath
- Aspirate and flush the left atrial sheath prior to introduction of the catheter
- Follow catheter introduction and use instructions described in the instructions for use
- Capture the spiral array in the capture device while submerged in a saline and/or heparinized saline bath
- Aspirate and flush left atrial sheath once catheter array is beyond the sheath valve to exclude air ingress.
- Resume continuous drip/flush of left atrial sheath

7.9.4 PVAC or PVAC GOLD pulmonary vein ablation

- Follow instructions described in the catheter instructions for use and generator operator manual
- Map for pulmonary vein potentials
- Initiate ablation in 4:1, 2:1, or 1:1 mode only
- Verify isolation of the pulmonary veins after 30 minutes

7.9.5 MASC catheter introduction

- Pause continuous drip/flush of left atrial sheath
- Aspirate and flush the left atrial sheath prior to introduction of the catheter
- Follow catheter introduction and use instructions described in the instructions for use
- Capture the array in the capture device while submerged in a saline and/or heparinized saline bath
- Aspirate and flush left atrial sheath once catheter array is beyond the sheath valve to exclude air ingress.
- Resume continuous drip/flush of left atrial sheath

7.9.6 MASC septal ablation

- Follow catheter introduction and use instructions described in the instructions for use
- Map for arrhythmogenic tissue
- Initiate ablation in 1:1 ablation mode only
- Verify elimination of arrhythmogenic tissue

7.9.7 MAAC catheter introduction

- Pause continuous drip/flush of left atrial sheath
- Aspirate and flush the left atrial sheath prior to introduction of the catheter
- Follow catheter introduction and use instructions described in the instructions for use
- Capture the array in the capture device while submerged in a saline and/or heparinized saline bath

- Aspirate and flush left atrial sheath once catheter array is beyond the sheath valve to exclude air ingress.
- Resume continuous drip/flush of left atrial sheath

7.9.8 MAAC CFAE ablation

- Follow catheter introduction and use instructions described in the instructions for use
- Map for arrhythmogenic tissue
- Initiate ablation in 1:1 ablation mode only
- Verify elimination of arrhythmogenic tissue

7.9.9 Post-procedure evaluation

- 12 lead ECG
- Resume vitamin K antagonist (VKA) anticoagulation per subjects existing dose schedule
- Check INR at minimum every 12 hours until INR is ≥ 2.0

7.10 Discharge follow-up

- Physical Exam
- Neurologic evaluation
  - It is strongly recommended that the neurological evaluation be conducted after the effects of anesthesia subside
  - If evaluation identifies focal or global neurological deficit and/or signs/symptoms suggestive of stroke; then the following assessments are required:
    - NIHSS
    - MMSE
    - mRS
- 12 lead ECG
- Review of arrhythmic symptoms
- INR*
- Concomitant medications
- [redacted]

***NOTE: subject cannot be discharged until INR is greater than or equal to 2.0 as per the HRS Consensus statement** (*After removal of all sheaths, warfarin should be reinitiated within four to six hours, and low-molecular weight heparin (LMWH) (enoxaparin 0.5–1.0 mg/kg twice daily) or intravenous heparin should be used as a bridge to resumption of INR 2.0 –3.0*).

7.11 30 day follow-up

NOTE: 30 day follow up visit should occur as close to day 30 following the ablation procedure without occurring prior to day 30.

- Physical Exam
- Neurologic evaluation
  - If evaluation identifies focal or global neurological deficit and/or signs/symptoms suggestive of stroke; then the following assessments are required:
    - NIHSS
    - MMSE
    - mRS
- 12 lead ECG
- Review of arrhythmic symptoms
- INR
- Concomitant medications
- [redacted]
- Cardioversion history

7.12 3 month follow-up

- Physical Exam
- Neurologic evaluation and assessments for subjects previously diagnosed with a focal or global neurological deficit and/or signs/symptoms suggestive of stroke; assessments include:
  - NIHSS
  - MMSE
  - mRS
- 12 lead ECG
- Review of arrhythmic symptoms
- INR
- Concomitant medications (amiodarone required to be stopped at this visit)
- Cardioversion history
- MRI or CT scan (Chest) for subjects in the PVS assessment cohort; subjects randomized to the PVS assessment cohort will receive a 3-month CT or MRI scan at their first 3-month post-ablation visit (e.g. if a subject is reablated after the initial 3-month post-ablation visit, a second CT scan for PVS screening is not required at the 3-month post-reablation visit). The same scanning technology should be used for the baseline and 3 month PVS assessment.
- [redacted]

7.13 6 month follow-up

- Physical Exam
- Neurologic evaluation and assessments for subjects previously diagnosed with a focal or global neurological deficit and/or signs/symptoms suggestive of stroke; assessments include:
    - NIHSS
    - MMSE
    - mRS
- 12 lead ECG
- 48 hour ambulatory ECG monitor. Note: the same ambulatory ECG monitoring technology used at the Baseline visit should be used at the 6-month follow-up visit. Subjects may be asked to repeat an ambulatory ECG monitoring session if less than 24 hours of analyzable monitoring time is obtained.
- Review of arrhythmic symptoms
- INR
- Concomitant medications
- Cardioversion history

7.14 Unscheduled follow-up visits

An unscheduled visit is defined as any unplanned office visit at the study site that occurs between protocol required visits. The requirements at an unscheduled visit are:

- Physical Exam
- Neurologic evaluation
    - If evaluation identifies focal or global neurological deficit and/or signs/symptoms suggestive of stroke; then the following assessments are required:
        - NIHSS
        - MMSE
        - mRS
- 12 lead ECG
- Review of arrhythmic symptoms
- INR
- Concomitant medications
- Cardioversion history

7.15 Permissible Retreatment Ablation Procedure

All study subjects may have one reablation procedure with the Phased RF System within 180 days of their index ablation procedure under this protocol if the following criteria are met:

- Subject has not completed the 6-month follow-up visit
- Recurrent AF/AFL that cannot be controlled with antiarrhythmic drugs and/or cardioversion
- The subject has not had any other ablation procedure in the left atrium since first Phased RF ablation
- Subjects undergoing a retreatment procedure are willing to be followed for 6-months following their retreatment procedure, or until official study closure defined as when Medtronic and/or regulatory requirements have been satisfied per the Clinical Investigational Plan, whichever occurs first. Medtronic will provide a new set of target visit dates following notification of a retreatment procedure as described in section 7.6.

7.16 Study Exit

All study subjects should complete the 6-month visit or official study closure, whichever comes first. Subjects may be exited from the study for any of the following situations:

- Subject has completed 6-month follow-up
- Medtronic and/or regulatory requirements have been satisfied per the Clinical Investigational Plan
- Subject lost to follow-up
- Subject death
- Subject did not meet inclusion/exclusion criteria
- Subject did not provide consent or data 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)

7.16.1 Lost to follow-up

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. In addition, follow the regulations set forth by the governing IRB/MEC. The study design accounts for possible lost to follow up and therefore those subjects will not be replaced.

7.16.2 Subject-initiated withdrawal

If subject chooses to withdraw, document reason for exit.

7.16.3 Early study suspension or termination

Medtronic may decide to suspend or prematurely terminate the study (e.g. if information becomes available that the risk to study subject is higher than initially indicated or because of other reasons). If the study is terminated prematurely or suspended, Medtronic shall promptly inform the clinical investigators of the termination or suspension and the reason(s) for this. The investigator shall then promptly inform the reviewing IRB/MEC and the study subjects or their legal representative. Subjects will be followed per clinical standard of care.

7.16.4 Early investigation site suspension or termination

Medtronic may decide to suspend or prematurely terminate an investigation site (e.g. in case of expiring approval of the reviewing MEC, non-compliance to the Clinical Investigation Plan or lack of enrollment). If an investigation site is suspended or prematurely terminated, Medtronic shall promptly inform the clinical investigator(s) of the termination or suspension and the reason(s) for this. The investigator shall then promptly inform the reviewing IRB/MEC and the study subjects or their legal representative. Subjects will be followed per clinical standard of care.

7.17 Study Closure

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

7.18 Concomitant Medications

All cardiovascular and vitamin K antagonist medications (as specified in Section 7.7 Study procedure details – Concomitant Medications) that subjects are prescribed at the time of the baseline visit will be documented on the concomitant medication log. At protocol defined study visits and any unscheduled visits; the concomitant medication log will be updated to reflect any changes in the subject's medications.

8. INVESTIGATIONAL DEVICE/SOFTWARE STORAGE, HANDLING AND TRACEABILITY

The Phased RF System is considered investigational in U.S. (GENius generator and components, PVAC or PVAC GOLD, MASC and MAAC) and Canada (MASC and MAAC only). In Europe, the Phased RF system is market released. In regions where the system is market released, the system will be used in the manner for which it was intended and it will not be considered as investigational.

U.S. and Canada

Investigational product will be distributed to a center only when Medtronic has received all required documentation and has notified the center of center activation. Distribution of the investigational product to study centers during the clinical study will be managed by Medtronic and can only be ordered by Medtronic personnel. Investigational product must be stored in a secure location at the site. It is the responsibility of the investigator to correctly handle, store, and track the investigational products. Investigational products will be used only in the study according to the CIP.

Europe

For geographies in which the product is market released, distribution of the product will be done by standard distribution methods.

All Geographies

Product Distribution logs will be automatically generated by the electronic data management system for tracking of all Phased RF products. The Product Distribution Logs are to be used for the *Phased RF System GENius generator, PVAC or PVAC GOLD, MASC and MAAC catheters, GENius JR remote and ECG interface box*. The logs must be maintained at each investigational center and updated when investigational product is received (U.S. and Canada only), opened, disposed of or returned to Medtronic

8.1 Final product disposition

All product should be returned to Medtronic for analysis when permissible by local laws and regulations. If the products are not returned, a justification is required to be reported on the appropriate case report form(s) or disposition log(s). The Product Distribution Log must be updated for all Phased RF products. To receive a Returned Product Mailer Kit, please contact your local Medtronic field personnel. All unused investigational product (U.S. and Canada Only) must be returned to Medtronic upon study closure at the center. The Product Disposition Log must be updated with the final device disposition.

Study sites in all geographies should return opened/used study devices as instructed by Medtronic.

9. STUDY DEVIATIONS

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

Prior approval by Medtronic is expected in situations where the investigator anticipates, contemplates, or makes a conscious decision to deviate. Prior approval is not required when a deviation is necessary to protect the 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).

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. However, prior approval from Medtronic is required for such situations. (Examples may include: unable to complete MRI due to claustrophobia).

All study deviations must be reported on the Case Report Form regardless of whether medically justifiable, pre-approved by Medtronic, an inadvertent occurrence, or taken to protect the subject in an emergency.

In the event the deviation involves a failure to obtain a subject's consent, or is made to protect the life or physical well-being of a subject in an emergency, the deviation must be reported to the Institutional Review Board (IRB) as well as Medtronic within five (5) working days. Reporting of all other study deviations should comply with MEC/IRB policies and/or local laws and must be reported to Medtronic as soon as possible upon the center becoming aware of the deviation. Reporting of deviations must comply with IRB/ MEC policies, local laws, and/or regulatory agency requirements. Refer to Investigator Reports, **Table 15**, **Table 16**, **Table 17** and **Table 18**, for geography-specific deviation reporting requirements and timeframes for reporting to Medtronic and/or regulatory bodies.

Medtronic is responsible for analyzing deviations, assessing their significance, and identifying any additional corrective and/or preventive actions (e.g. amend the Clinical Investigation Plan, conduct additional training, terminate the investigation). Repetitive or serious investigator compliance issues may result in initiation of a corrective action plan with the investigator and site, 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 site on a periodic basis.

Examples of study deviations include but are not limited to the following:

- IRB/MEC approval not obtained before starting the study
- IRB/MEC approval lapse during the study
- Subject enrolled during lapse of IRB/MEC approval
- Informed consent not obtained prior to participation in the study
- Incorrect version of the consent form provided to the subject

- Control of investigational product not maintained or inadequate
- Unauthorized use of an investigational product outside of the study
- Adverse event not reported by investigator in the required regulatory time frame
- Enrolled subject did not meet inclusion/exclusion criteria
- Visit outside of the protocol defined window
- Visit not completed
- Protocol-required testing or programming not done
- Source data permanently missing (i.e., hospital/clinic records)
- Unauthorized physician or study personnel performing study procedures

10. ADVERSE EVENTS AND DEVICE DEFICIENCIES

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

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

There are no adverse event (AE) stopping rules tied to the collection and reporting of AEs for this study, except for those rules identified in the regulatory requirements. However, if more than six (6) strokes that meet the definition of the primary safety endpoint as described in Table 5 occur prior to completing enrollment, the study may stop early for futility.

For any changes in status of a previously reported AE (i.e. change in action, change in outcome, change in relatedness, change in seriousness), an AE update must be completed.

All AEs must be followed until resolved, ongoing without further actions to be taken, 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 ongoing AEs are resolved or they are ongoing without further actions to be taken.

10.1 Adverse Event and Device Deficiency Assessment

All new and/or worsened AE information will be collected throughout the study duration, starting at subject enrollment, and reported to Medtronic on electronic case report forms (e-CRFs).

Events that do not qualify as AEs:

- Documented pre-existing conditions without a change in the nature or severity of the condition including recurrent AF or atrial flutter following a Phased RF procedure provided symptom severity does not increase relative to baseline
- Unavoidable adverse events (see Table 9)
- Inability to successfully complete ablation procedure, unless injury occurs
- An undesirable device event that does not result in a medically undesirable situation for the subject (device deficiency)
- Non symptomatic arrhythmia episodes
- [redacted]

Events that do not qualify as Serious Adverse Events:

- Cardioversions (DC or Drug) for recurrent symptomatic atrial fibrillation is not considered a serious adverse event

In all geographies, Unavoidable AEs, listed in Table 9 need not be reported unless the AE worsens or is present outside the stated timeframe post-procedure, if required per local regulations.

Table 9: Unavoidable Adverse Events Related to Ablation Procedure

Event Description	Time Frame (Hours) from the Surgical Procedure
Anesthesia related nausea/vomiting	24
Low-grade fever (<100°F or < 37.8°C)	48
Groin insertion/site pain	72
Mild to moderate bruising / ecchymosis	168
Sleep problems (insomnia)	72
Back pain related to lying on the table	72
Chest pain secondary to ablation (during procedure)	4

Foreseeable Adverse Events

The Phased RF system used within the VICTORY AF study is currently market released in Europe. Foreseeable adverse event information associated with the Phased RF System is provided in the Phased RF catheter device labeling that is included with each ablation catheter. Additionally, information related to recent clinical experience can be found in the report of prior investigations.

10.2 Adverse Event and Device Deficiency Definitions, Classification and Reporting

Adverse Event Classification and Reporting

AEs will be classified according to the classifications and definitions provided. In order to meet the requirements of the regulatory agencies (RA), each event will be classified by the investigator according to the standard regulatory definitions as outlined in Table 10. Where the definition in Table 10 (with the exception of the system relatedness section) indicates “device”, it refers to any device used in the study. This might be the device, or any market released component of the system.

AE reporting must be completed according to local regulatory requirements as well as per reporting detailed in Tables 12 and 13, as applicable.

It is the responsibility of the investigator to abide by the adverse event reporting requirements stipulated by the site’s Investigational Review Board (IRB)/ Medical Ethics Committee (MEC)

Upon sponsor receipt of AEs, a sponsor study team member will review the AE for completeness and accuracy and when necessary will request clarification and/or additional information from the investigator. Sponsor will utilize the Medical Dictionary for Regulatory Activities (MedDRA) to assign a MedDRA term for each AE based on the information provided by the investigator.

For emergency contact regarding AEs, contact a Medtronic Clinical Research Specialist immediately. Study contact information is provided in the CIP as well as in the center’s study documents binder/investigator site file and will be updated if contact information changes.

Vigilance activities will be conducted in parallel and, if possible, in conjunction with the CEC activities to ensure adherence to the required reporting timelines.

Reporting of Device Deficiencies

Device deficiencies that did not lead to an AE but could have led to a serious adverse device effect (SADE)

a) if either suitable action had not been taken,
b) if intervention had not been made, or
c) if circumstances had been less fortunate require immediate reporting (see Table 13).
Initial reporting may be done on the CRF completing as much information as is available. The original completed Device Deficiency CRF must be sent to Medtronic as soon as possible.

Adverse Event and Device Deficiency Review Process
All adverse events and device deficiencies will be reviewed by Medtronic. This review will include the determination of whether the adverse event/device deficiency meets regulatory reporting requirements. The sponsor will ensure timely adverse events/device deficiency reporting to meet global regulatory requirements. In case the adverse event/device deficiency is related to a market approved/released device used during the study, Medtronic will immediately report this device related adverse event/device deficiency to the Medtronic Complaint Handling Unit and ensure prompt review, and appropriate reporting.

Table 10: Adverse Event and Device Deficiency Definitions

Definition	Description
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. (ISO14155:2011 3.2) *NOTE 1*: This definition includes events related to the investigational medical device or the comparator. *NOTE 2:* This definition includes events related to the procedures involved. *NOTE 3:* For users or other persons, this definition is restricted to events related to investigational medical devices.
Adverse Device Effect (ADE)	Adverse event related to the use of an investigational medical device. (ISO14155:2011 3.1) *NOTE 1:* This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. *NOTE 2:* This definition includes any event resulting from use error or from intentional misuse of the investigational medical device

Unavoidable AE	An adverse event inherent to a surgical procedure that is expected to occur in all subjects for a projected duration.
Seriousness	
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, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the CIP or application (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))
Serious Adverse Event (SAE)	An adverse event that a) led to a death, b) led to a serious deterioration in the health of the subject that either resulted in • a life-threatening illness or injury, or • a permanent impairment of a body structure or a body function, or • in-patient or prolonged hospitalization, or • medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or a body function c) led to fetal distress, fetal death or a congenital abnormality or birth defect. (ISO 14155:2011 3.37) *NOTE: Planned hospitalization for a preexisting condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.*
Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. (ISO 14155:2011 3.36)
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. (ISO 14155:2011 3.42) 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.

Complication	An adverse event that results in death or requires invasive intervention. Non-invasive: when applied to a diagnostic device or procedure, means one that does not by design or intention: Penetrate or pierce the skin or mucous membranes of the body, the ocular cavity, or the urethra, or Enter the ear beyond the external auditory canal, the nose beyond the nares, the mouth beyond the pharynx, the anal canal beyond the rectum, or the vagina beyond the cervical os. For purposes of this part, blood sampling that involves simple venipuncture is considered noninvasive, and the use of surplus samples of body fluids or tissues that are left over from samples taken for non-investigational purposes is also considered noninvasive. (21 CFR 812).
Observation	Any adverse event that is not a complication.
Device Deficiency	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance (ISO 14155:2011 3.15) *NOTE:* Device deficiencies include malfunctions, use errors, technical observations and inadequate labeling.
Relatedness	
System Related	An adverse event that results from the presence or performance (intended or otherwise) of the system component. • **Catheter Related:** An adverse event that results from the presence or performance (intended or otherwise) of the Phased RF catheters • **Generator Related:** An adverse event that results from the presence or performance (intended or otherwise) of the Phased RF generator
Procedure Related	An adverse event that occurs due to index or reablation procedure.
Cardiovascular Related	An adverse event related to the heart and blood vessels or the circulation.
Neurologic related	An adverse event related to neurologic deficit
Timing	
Pre-procedure AE	An adverse event that occurs after the patient informed consent form has been signed and on the day of the Phased RF procedure, but prior deployment of Phased RF catheters in left atrium.

During procedure AE	An adverse event that occurs during procedure, after deployment of Phased RF catheters in the left atrium.
Post-procedure AE	An adverse event that occurs after removal of Phased RF catheters from the left atrium.
Other	
Hospitalization	A therapeutic inpatient hospitalization (excludes outpatient and emergency room visits) lasting greater than or equal to 24 hours.
Stroke	Hemorrhagic and Ischemic stroke with rapid onset of a focal or global neurological deficit or other neurological signs/symptoms consistent with stroke
Stroke Symptom Duration	Duration of focal or global neurological deficit ≥24 hours; **OR** Duration of focal of global neurological deficit <24 hours **IF:** • Therapeutic interventions • Thrombolytic therapy • Intracranial angioplasty **OR** • Neuroimaging documents a new hemorrhage or infarct **OR** • Neurological deficit results in death
Stroke Periprocedural Definition	Within 30 days of Phased RF catheter ablation procedure in which Phased RF catheter was deployed in the left atrium
Stroke Diagnosis	Appropriate diagnostics will be determined by the site's neurologist's clinical evaluation and include one or more of the following: • Clinical signs and symptoms consistent with focal or global neurologic deficit • Neuroimaging procedure (CT or MR scan or cerebral angiography) • Lumbar puncture (i.e. subarachnoid hemorrhage) **AND** Adjudicated as peri-procedural stroke by Clinical Events Committee
Transient Ischemic Attack (TIA)	New focal neurological deficit with rapid symptom resolution (usually 1 to 2 h), always within 24 h without tissue injury (based on neuroimaging)

Table 11: Adverse Event Classification Responsibilities

What is Classified	Who Classifies	Classification Parameters
Timing of the Event	Investigator	Pre-procedure, procedure or Post-procedure
Relatedness	Investigator	System Related, Procedure Related, Neurologic related, Cardiovascular Related[3]
Seriousness	Investigator	Unanticipated Adverse Device Effect, (UADE), Unanticipated Serious Adverse Device Effect (USADE), Serious Adverse Event, Serious Adverse Device Effect,
	Sponsor	Unanticipated Adverse Device Effect, Complication or Observation for system, procedure adverse events only[1]
Diagnosis	Investigator	Based on presenting signs and symptoms and other supporting data
	Sponsor	MedDRA term assigned based on the data provided by Investigator[2]
Death Classification	Investigator	Sudden Cardiac, Non-sudden Cardiac, Non-cardiac, Neurologic, Unknown[4]

[1] The CEC will further adjudicate system and procedure related AEs for complication/observation.
[2] The CEC will not adjudicate the following: UADE, USADE, timing of the event, or the MedDRA code.
[3] The CEC will adjudicate all AEs for cardiovascular relatedness and neurologic relatedness
[4] CEC will adjudicate deaths to relatedness and death classification. All other adjudication information for deaths will be taken from the corresponding AE with the outcome of death.

Subject Death
All subject deaths must be reported by the investigator to the sponsor as soon as possible after the investigator first learns of the death. Report the Adverse Event, documenting the event resulting in the subject's death.

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

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

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 definitions provided in Table 12.

Table 12: Death Classification Definitions

Death Classification Definitions	
Cardiac Death[1]	A death directly related to the electrical or mechanical dysfunction of the heart.
Sudden Cardiac Death (SCD)	Natural death due to cardiac causes, heralded by abrupt loss of consciousness within one hour of the onset of acute symptoms; preexisting heart disease may have been known to be present, but the time and mode of death are unexpected. If time of onset cannot be determined, SCD will alternatively be defined as any unexpected cardiac death occurring out of the hospital or in the emergency room as dead on arrival.
Non-sudden Cardiac Death	All cardiac deaths that are not classified as sudden deaths, including all cardiac deaths of hospitalized subjects on inotropic support.
Non-cardiac Death	A death not classified as a cardiac death.
Neurologic Death	A death due to neurologic deficit
System Related	A death that results from the presence or performance of any component of the study system.
Procedure Related	A death that occurs due to any procedure related to the ablation procedure.
Unknown	Unknown death classification is intended for use only when there is insufficient or inadequate information to classify the death

[1] Cardiac Death will only be used as reference for other classifications.

Regulatory reporting of subject deaths will be completed according to local regulatory requirements. Refer to Table 13 for a list of required investigator and sponsor reporting requirements and timeframes.

10.3 Clinical Events Committee Review

At regular intervals, an independent Clinical Events Committee (CEC) will review all adverse events and deaths.

The CEC will consist of a minimum of three (3) non-sponsor employed physicians (including one vascular neurologist and one electrophysiologist), and the CEC chairperson. The CEC members will not include participating VICTORY AF investigators. The purpose of the CEC is to conduct a medical review of events for subjects participating in the study. At least three CEC members must adjudicate, at a minimum, all deaths, all neurologic events, and all AEs related to any component of the system. All other AEs will be adjudicated by at least one physician member of the CEC.

Sponsor personnel may facilitate and participate in CEC meetings but will be non-voting members. The sponsor will provide the CEC with the investigator's description and classification of each AE in addition to sponsor's assignment of the MedDRA key term. Additionally, the sponsor's assignment of the complication or observation classification will be provided for all system and procedure related AEs. The CEC is responsible for reviewing the investigator's assessment and classification of each event. The CEC will review adverse events and provide a final adjudication of relatedness and seriousness as applicable for all events as well as the complication/observation classification for system or procedure related events. In addition, the CEC will determine the cardiovascular and neurological relatedness of each AE. 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, this will be documented accordingly. If the investigator does not agree with the CEC classification, both determinations will be documented within the study report. However, the CEC determination will be used for analysis purposes.

Additionally, the CEC will determine whether each AE meets the definition of a procedure and/or device related stroke in Table 5 or the TIA definition in Table 10.

10.4 Steering Committee (SC)

The steering committee will be an advisory body to the VICTORY AF study team and be responsible for collaboration and guidance on study goals, design, study center communications, training materials and other activities based on expertise or as agreed upon.

The study's steering committee (SC) will be comprised of non-Medtronic physicians including at least one EP and one neurologist.

10.5 Data Monitoring Committee (DMC)

Ongoing oversight for this study will be provided by an independent DMC. The DMC will consist of a minimum of at least one electrophysiologist, one neurologist, and one statistician who are not sponsor employees. The DMC will not include participating VICTORY AF investigators, members of the Steering Committee or Clinical Events Committee.

The DMC is retained to aid the sponsor in safeguarding the interests of trial participants and monitoring the overall conduct of the study. The DMC will meet at regular intervals or as

agreed upon to review accumulating study data and will be advisory to the sponsor and may provide recommendations for early termination of the trial. Review and consensus by the entire committee is required to recommend that the study should be stopped. The DMC may also make recommendations related to the selection, management and retention of subjects, improvement of adherence to protocol-specified regimens, and procedures for data management and quality control.

10.6 Market Released Event Reporting

The following definitions apply to all market released products used in the clinical study and must be reported according to standard market release reporting guidelines per geography.

Medical Device Reporting (MDR) Requirements for User Facilities (U.S.)
General Reminder for Investigators:
Per FDA regulations, Device User Facilities are required to report Medical Device Reports (MDR) on market approved products (21 CFR 803, subpart C) A Device User Facility is defined as a hospital, an ambulatory surgical facility, a nursing home, an outpatient treatment facility, or an outpatient diagnostic facility which is not a physician's office.

Vigilance Reporting (EEA)
It is the responsibility of the investigator to report all product complaints and misuse and abuse immediately via the regular channels for CE marked products. The reporting of product complaints abuse, and misuse of these CE-labeled devices is not part of the clinical study and should be done in addition to the AE reporting requirements.

10.7 Investigator Adverse Event and Device Deficiency Recording and Reporting Requirements

AEs and device deficiencies will be recorded and reported according to local regulatory requirements. Refer to Table 13 AE requirements. It is the responsibility of the Investigator to abide by the adverse event reporting requirements stipulated by the centers' IRB/MEC.

Table 13: Adverse Event and Device Deficiency Reporting Requirements

Serious Adverse Events (SAEs)	
Investigator submit to:	
Medtronic	**Europe:** Immediately after the investigator first learns of the event or new information in relation with an already reported event. (ISO 14155 and local law) **All other geographies:** Submit in a timely manner after the investigator first learns of the event.
Ethics Board	**Europe:** Submit to Ethics Board per local reporting requirement **All other geographies:** Submit per local EC requirement.
Sponsor submit to:	
Regulatory authorities	**Europe:** Submit to Competent Authority per local reporting requirement.
Ethics Board	**Europe:** Submit to Ethics Board per local reporting requirement.
Serious Adverse Device Effects (SADEs)	
Investigator submit to:	
Medtronic	**Canada:** Investigators are required, per the TPD Investigator Agreement, to report any incident that is related to a failure of the device or deterioration in its effectiveness, or any inadequacy in its labeling or directions for use leading to death or serious deterioration in a subject's health within 72 hours after the occurrence. (Canada Medical Device Regulations, SOR/98-282; 77, 59) **Europe:** Immediately after the investigator first learns of the event. (ISO 14155 and local law) **All other geographies:** Submit in a timely manner after the investigator first learns of the event.
Ethics Board	**Europe:** Inform Ethics Board about any SADE (ISO 14155) Reporting timeframe as per local MEC requirement. **All other geographies:** Submit per local Ethics Board requirement.
Health Canada	**Canada:** Investigators are required, per the TPD Investigator Agreement, to report any incident that is related to a failure of the device or deterioration in its effectiveness, or any inadequacy in its labeling or directions for use leading to death or serious deterioration in a subject's health within 72 hours after the occurrence. (Canada Medical Device Regulations, SOR/98-282; 77, 59)
Sponsor submit to:	
Regulatory authorities	**Canada:** Preliminary and final reporting to the Canadian Ministry of Health 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 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)) **Europe:** Reporting timelines as per local competent authority.

Ethics Board	**Canada and Europe:** Submit per local requirement (ISO 14155)
Unanticipated Adverse Device Effects (UADEs) and Unanticipated Serious Adverse Device Effects (USADEs)	
Investigator submit to:	
Medtronic	**Canada:** Investigators are required, per the Therapeutic Products Directorate Investigator Agreement, to report any incident that is related to a failure of the device or deterioration in its effectiveness, or any inadequacy in its labeling or directions for use leading to death or serious deterioration in a subject's health within 72 hours after the occurrence. (Canada Medical Device Regulations, SOR/98-282; 77, 59) **Europe:** Immediately after the investigator first learns of the effect. (ISO 14155 and local law) **US:** Submit as soon as possible, but no later than within 10 working days after the investigator first receives notice of the effect. (21 CFR 812.150(a)(1)) **All other geographies:** Submit in a timely manner after the investigator first learns of the effect.
Ethics Board	**US:** Submit as soon as possible, but no later than within 10 working days after the investigator first receives notice of the effect. (21 CFR 812.150(a)(1)) **All other geographies:** Reporting timeframe as per local Ethics Board requirement.
Health Canada	**Canada:** Investigators are required, per the TPD Investigator Agreement, to report any incident that is related to a failure of the device or deterioration in its effectiveness, or any inadequacy in its labeling or directions for use leading to death or serious deterioration in a subject's health within 72 hours after the occurrence. (Canada Medical Device Regulations, SOR/98-282; 77, 59)
Sponsor submit to:	
Investigator	**All geographies:** Notification as soon as possible, but not later than 10 working days after the sponsor first learns of the effect. (21 CFR 812.150(b)(1))
Regulatory authorities	**Canada:** Preliminary and final reporting to the Canadian Ministry of Health 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 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)) **Europe**: All UADEs are classified as SADEs and should follow the applicable reporting requirements. (ISO 14155) and Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95 3.A.1) Reporting timeframe as per local competent authority .(ISO 14155:2011 3.42) **US:** Notification as soon as possible to FDA, but not later than 10 working days after the sponsor first receives notice of the effect. (21 CFR 812.150(b)(1))
Ethics Board	**All geographies:** Notification as soon as possible, but not later than 10 working days after the sponsor first learns of the effect. (21 CFR 812.150(b)(1))
All other reportable Adverse Events (system, procedure and cardiovascular-related)	
Investigator submit to:	
Medtronic	**All geographies:** Submit in a timely manner after the investigator first learns of the event.
Regulatory authorities	**All geographies:** Submit or report as required per local reporting requirement.

Ethics Board	**All geographies:** Submit per local Ethics Board requirement.
Device Deficiencies with 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. **All other geographies:** Submit or report as required per local reporting requirements.
Ethics Board	Submit per local EC requirement.
Regulatory authorities	Report immediately after the investigator first learns of the event if required according to local law.
Sponsor submit to:	
Regulatory authorities	**All geographies:** Submit or report as required per local reporting requirements.
Ethics Board	**All geographies:** Submit per local Ethics Board requirement.
All other Device Deficiencies	
Investigator submit to:	
Medtronic	**All geographies**: Submit in a timely manner after the investigator first learns of the deficiency.
Regulatory Authorities	**All geographies**: Submit or report as required per local reporting requirement.
EC	**All geographies**: Submit per local EC requirement.

11. RISK ANALYSIS

The residual risks associated with the Phased RF System have been found to be acceptable and have been mitigated to the fullest extent possible. The potential benefits related to the use of the Phased RF System have been determined to outweigh any potential risks.

For geographies where the study devices are market-approved, there are no known incremental risks to the study subject as a result of participating in the study. These risks are documented in the product labeling. However, there are potential risks and side effects associated with an ablation and required study follow-up procedures (e.g. CT and/or MRI scans for [redacted] PV stenosis [redacted]). These risks are provided in the Informed Consent Form.

Table 14 describes the potential risks that have been identified since the TTOP-AF study and the mitigations that have been put in place to minimize the risks.

Table 14: Potential Risks and Risk Minimization

Potential Risks	Risk Minimization
Peri-procedural stroke	Based on literature review (provided Executive Summary and Report of Prior Investigations), the continuance of oral anticoagulation prior, during and post ablation procedure reduces the risks of stroke without increasing the risk of bleeding complications, particularly with therapeutic INR (2.0-3.5). Maintaining procedural ACT >350 has also been associated with reduced stroke incidence. Rigorous sheath management during catheter introduction and exchanges has demonstrated a reduced likelihood of air egress during the ablation procedure.

Potential Risks	Risk Minimization
[redacted]	[redacted]
Pulmonary vein stenosis	Physician operators will be trained on visualization techniques (e.g. fluoroscopy imaging in LAO and RAO views depending on pulmonary vein target) to verify the PVAC or PVAC GOLD catheter is not situated within the tubular portion of the PV prior to ablation.

11.1 Risk-to-Benefit Analysis

The cohort of subjects for inclusion in this study is symptomatic as a result of their persistent atrial fibrillation and the failure of class I or III antiarrhythmic drug therapy. Phased RF ablation therapy offers the opportunity to reduce the episodes of atrial fibrillation and therefore reduce symptoms. Catheter ablation therapy in subjects with paroxysmal atrial fibrillation have shown improvements in symptoms and reduced episodes of atrial fibrillation.

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

In Europe, Phased RF ablation catheters are approved to treat subjects with persistent atrial fibrillation. If successful, the VICTORY AF study could confirm meaningful therapeutic benefit in this underserved population.

12. STATISTICAL METHODS AND DATA ANALYSIS

Medtronic employees or their designated representatives will perform all statistical analysis.

Additionally, a separate Statistical Analysis Plan (SAP) will be developed to further describe statistical methods, pre-specified data handling rules, and pre-specified analyses that will be included in study reports (e.g. PMA report, final study report).

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

The study will be considered successful if the primary objective is met. Specifically, for the study to be successful, the observed procedure and/or device related stroke rate must be less than 1.8% and its associated exact one-sided upper 95% confidence interval must be less than 3.5%.

12.1 General Summaries

12.1.1 Description of Baseline Variables

Standard baseline and relevant medical history will be collected on the CRFs for all enrolled subjects. Baseline variables to be summarized include, but are not limited to: age, sex, race, physical exam findings, arrhythmia history, arrhythmic symptoms, baseline ECG interpretation, AF medication history, baseline MMSE score, baseline $CHADS_2$ score and CHA_2DS_2-VASc.

For continuous variables, mean standard deviation, median, and range will be reported. For categorical variables, frequency and percentage will be reported. Summaries of baseline information and relevant medical history will be summarized for all enrolled subjects, all subjects with a Phased RF ablation procedure (e.g. at least one Phased RF catheter placed in the left atrium), subjects randomized to the PVS assessment cohort [redacted]

12.1.2 Summary of Ablation Procedures

A summary of Phased RF ablation procedure information including procedure times, ablation locations, Phased RF ablation catheters used, and ablation energy modes will be summarized for procedures where at least one Phased RF ablation catheter was placed in the left atrium.

12.1.3 PVAC and PVAC GOLD catheter use

If Phased RF ablation procedures are performed with more than one PVAC model, subgroup analyses will be performed on the primary and secondary

objectives [redacted] by PVAC model. Specifically, should the need for a subgroup analysis occur, three subgroups will be defined as subjects ablated with only the PVAC catheter (index and reablation procedure), subjects ablated with only the PVAC GOLD catheter (index and reablation procedure), and subjects ablated with both the PVAC and PVAC GOLD catheter (e.g. index procedure with PVAC catheter and reablation procedure with PVAC GOLD catheter). For each of these objectives, Fisher's Exact test would then be used to assess the heterogeneity of the results by PVAC catheter subgroup should the need for a subgroup analysis arise.

12.2 Primary Objective: 30-day procedure and/or device related stroke rate

12.2.1 Objective

Demonstrate that the observed incidence of procedure and/or device related incidence of new stroke (excludes transient ischemic attack) within 30 days of an ablation procedure (index or reablation) with the Phased RF System is less than 1.8% with observed upper confidence boundary that is less than 3.5%.

12.2.2 Hypothesis

To pass the primary objective the following two conditions must be met:

1. The observed procedure and/or device related stroke rate must be less than 1.8%.
2. The exact one-sided upper 95% confidence interval for the procedure and/or device related stroke rate must be less than 3.5%.

The formal statistical hypothesis for the primary objective is:
H_o: $\pi \geq 3.5\%$
H_a: $\pi < 3.5\%$

where π is the true 30-day post ablation procedure (index or reablation) procedure and/or device related stroke rate.

12.2.3 Definition of procedure and/or device related stroke

Procedure and/or device related strokes are defined as events classified by the CEC meeting all of the requirements in Table 5. Specifically, the stroke must have a symptom onset date within 30 days of an ablation procedure where at least one phased RF catheter is deployed into the left atrium and be considered related to the procedure and/or device by the CEC.

12.2.4 Rationale for stroke threshold

The peri-procedural stroke rate is not well characterized in the persistent and long-standing persistent AF population. The observed procedure or device related stroke rate among the 176 ablated subjects in the TTOP-AF study was

2.8% with an upper one-sided 95% confidence interval of 5.9%. However, the FDA Center for Devices and Radiological Health's cardiac devices advisory panel indicated that both the observed stroke rate and its associated upper confidence boundary in the TTOP-AF study were too high to enable approval of the phased RF ablation system. Medtronic has identified several mitigation strategies that are expected to lower the peri-procedural stroke rate. With these mitigation strategies enforced in the current protocol, Medtronic believes the true procedure and/or device related peri-procedural stroke rate will be less than 1.8%, a value similar to the peri-procedural stroke rates reported in recent observational studies.

Specifically, a single site registry study by Patel et al., reported a 1.8% per-procedural stroke rate (one-sided upper 95% CI: 2.6%) among 1209 subjects with persistent or long-standing persistent AF undergoing off label AF ablation. Additionally, Patel et al. found that persistent AF was the only independent predictor of peri-procedural stroke risk in a multivariable analysis. A similar study was performed by Spragg et al, evaluating 517 subjects with atrial fibrillation. The stroke rate was 1.7% (95% one-sided UCB; 3.8%) for the 240 subjects with persistent atrial fibrillation. A key limitation with these observational trials is that the studies' did not require rigorous follow-up protocols and therefore the stroke rates may be under reported.

After considering all available data sources together with close consultation with the FDA, a procedure and/or device related peri-procedural stroke threshold of 3.5% was chosen. This threshold is greater than the upper one-sided 95% confidence intervals reported by Spragg et al and Patel et al but is lower than the upper confidence interval for the peri-procedural stroke rate observed in the TTOP-AF study. Additionally, a peri-procedural stroke threshold of 3.5% mandates that the observed study stroke rate must be less than 1.8% for study success for a sample size of at least 300 ablated subjects.

12.2.5 Experimental design and analysis methods

This study is a prospective, unblinded, multi-center, worldwide clinical study designed to evaluate the procedure and/or device related peri-procedural stroke rate within 30 days of an ablation procedure with the Phased RF System. The study will be considered successful if the primary objective is met. A single decision regarding study success will be made once all subjects with a Phased RF ablation procedure have had the opportunity for a reablation procedure (completed the 6-month visit) or completed the 30-day post-reablation visit if a reablation is required. Alternatively, the study may stop early for futility if more than six (6) procedure and/or device related peri-procedural strokes occur prior to completing enrollment.

For computing the peri-procedural stroke rate, the denominator will be all subjects with at least one ablation procedure attempt where at least one of the Phased RF catheters was deployed into the left atrium and have at least 30 days of post-

procedure follow-up. Also, subjects who have a procedure and/or device related peri-procedural stroke as classified by the CEC with symptom onset date within 30 days of a Phased RF ablation procedure will be included. The numerator for the stroke rate will be all subjects included in the denominator that had a procedure and/or device related stroke as classified by the CEC with a symptom onset date within 30 days of a Phased RF ablation procedure. The null hypothesis will be rejected in favor of the alternative if the observed stroke rate is less than 1.8% and the exact one-sided upper 95% confidence interval is less than 3.5%.

Additionally, a one-sided exact p-value will be computed for comparing the observed stroke rate to the performance goal of 3.5%.

12.2.6 Sample size and power

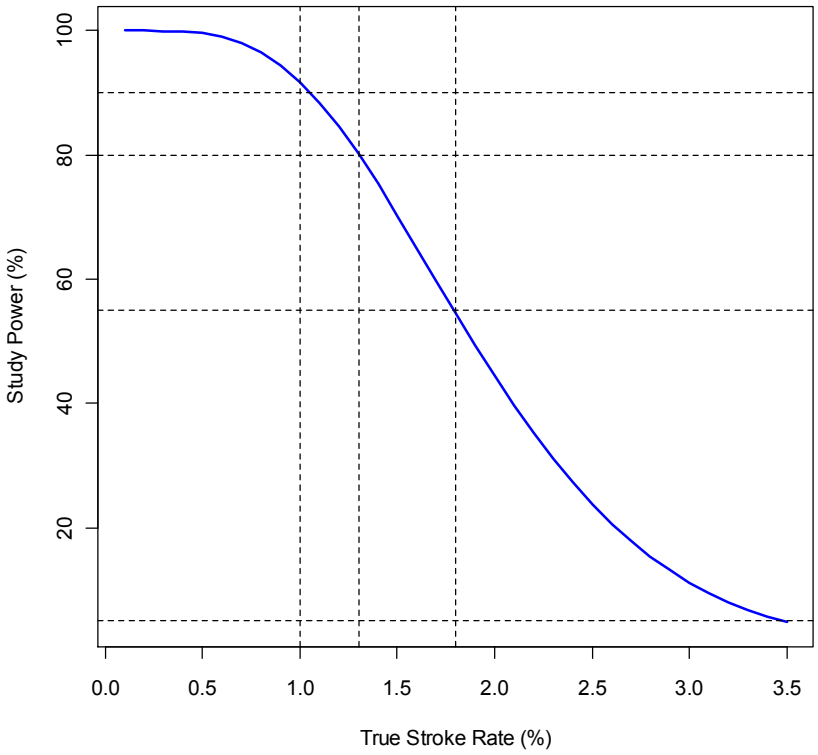
A sample size of 300 subjects completing the 30-day post procedure follow-up visit and having the opportunity for a reablation procedure (i.e. completing the 6-month follow-up visit) or having a reablation procedure and completing the 30-day post-reablation visit provides at least 80% power to test the primary study hypothesis given the following assumptions:

1. One-sided type I error rate of 0.05
2. Exact test of a binomial proportion versus a fixed performance goal of 3.5%
3. Observed stroke rate must be less than 1.8%.
4. Assumed true stroke rate is 1.3%

Figure 1 displays the power of the study to meet its primary objective when the true stroke rate ranges from 0.1% to 3.5% and 300 subjects complete the 30-day post-ablation (or reablation) visit and have had the opportunity for a reablation procedure. Specifically, the study has 90% power if the true stroke rate is 1%, 80% power if the true stroke rate is 1.3%, and 55% power if the true stroke rate is 1.8%. Figure 1 also demonstrates that the type I error is less than 5% when the true stroke rate is 3.5%.

Assuming an annualized attrition rate of 10% following the index ablation procedure, a uniform reablation rate of 30% within 180 days of the index ablation procedure, and a conservative 26% pre-procedure attrition rate up to 420enrolled subjects will be required to ensure that at least 300 subjects complete the 30-day post ablation follow-up visit and have the opportunity for a reablation procedure or have a reablation procedure and complete the 30-day post-reablation procedure visit. Note that it is not anticipated that all 420 subject enrollments will be required, since study enrollment will cease once enough subjects have completed an index Phased RF procedure to ensure that the target sample size of 300 evaluable subjects can be obtained.

Figure 1: Study Power versus True Stroke Rate



12.2.7 Determination of subjects for analysis

All subjects with at least one attempted ablation procedure with the Phased RF system where at least one investigational catheter was deployed into the left atrium and have completed at least 30 days of post-procedure follow-up will be included in the analysis. Additionally, all subjects with a procedure and/or device related stroke as classified by the CEC with a symptom onset date within 30 days of a procedure where a Phased RF catheter was placed in the left atrium will be included in the analysis regardless of whether the subject has less than 30 days of post-procedural follow-up.

In the rare instance where a subject has a non-investigational ablation catheter placed in the left atrium, the subject will be excluded from the analysis of the primary objective. However, a summary of all peri-procedural AEs will be provided for any subject excluded from the primary analysis.

12.2.8 Missing data

The impact of missing data on the analysis of this objective is expected to be small since only a 30 day post-ablation follow-up period is required. However, missing data could arise if a subject undergoes a Phased RF ablation procedure, does not have procedure and/or device related peri-procedural stroke, and exits the study

prior to their 30 day post-procedure visit. These subjects will not be included in the primary analysis cohort, but a tipping point analysis will be employed to determine the impact of the missing data on the observed stroke rate should the issue of missing data arise.

Another potential source of missing data comes from subjects that do not have a stroke following the index procedure, but exit the study following the 30-day post-index ablation visit, but prior to the 6-month visit or a reablation procedure. These subjects are included in the primary analysis as not having a stroke since no stroke was observed following the index ablation procedure. However, a tipping point analysis will be conducted to determine the plausibility these subjects could change the outcome of the study across a range of reablation rates and reablation stroke rates.

12.2.9 Pre-specified Subgroup analyses

The procedure and/or device related stroke rate will be displayed separately by gender (male/female), AF type (persistent/long-standing persistent), age (≤70 years, >70 years), and region (US/non-US). Due to the small number of expected peri-procedural strokes, the study is not powered for these subgroup analyses, however, for these analyses, point estimates and exact one-sided 95% upper confidence intervals will be computed within each subgroup.

12.2.10 Analysis Timing

A visit cutoff date will be defined as the maximum of the last 6-month post-index ablation visit, last study exit, or last 30-day post-reablation procedure visit. The data from all visits and procedures meeting this visit cutoff date will be included in the analysis.

12.3 Secondary Objectives

12.3.1 Secondary Objective #1: 6-month Post-Procedural Effectiveness

12.3.1.1 **Objective**

Confirm the 6-month post-procedural effectiveness.

12.3.1.2 **Hypothesis**

There is no pre-specified hypothesis associated with this secondary objective.

Since the 6-month effectiveness of the Phased RF system was shown to be superior to optimal medical management in the TTOP-AF study and the primary purpose of this study is to evaluate the safety of the system there is no formal statistical hypothesis required for this objective. Thus, the main purpose for characterizing 6-month effectiveness is to demonstrate that study investigators are not overly cautious during the Phased RF procedure to optimize procedure safety.

12.3.1.3 **Definition of 6 Month effectiveness**

6-Month effectiveness will be defined as:

- Acute procedural success, AND
- $\geq$ 90% reduction in clinically significant AF/AFL by 48-hour ambulatory ECG monitor. Clinically significant AF/AFL is defined as; any AF/AFL episode lasting longer than 10 consecutive minutes in duration, AND
- Off amiodarone for at least 90 days and off all other class I and class III antiarrhythmic drugs for at least 60 days prior to the 6-month ambulatory ECG monitor, AND
- Free from DC cardioversion for AF for at least 60 days prior to the 6-month ambulatory ECG monitor

12.3.1.4 **Analysis Methods**

Acute effectiveness for each subject will be determined as described in section 12.3.2. In order for a subject to meet the acute procedural success criterion for the 6-month effectiveness endpoint, the subject must be an acute procedural success for their index and reablation procedure (if required). Ambulatory ECG monitor recordings will be completed at the baseline and 6-month post final Phased RF ablation visit. Ambulatory ECG recordings will be read and summarized by the Holter core laboratory. For the baseline and 6-month post-ablation procedure ambulatory ECG recording, the percentage of time in clinically significant AF (AF > 10 minutes) will be calculated as the total number of seconds in clinically significant AF divided by the total analyzable ambulatory ECG monitor recording time in seconds. The percent reduction from baseline will be calculated as the difference of the percentage of time in clinically significant AF between the baseline and 6-month post-ablation procedure visit divided by the percentage of clinically significant AF at baseline. Subjects with at least a 90% reduction in clinically significant AF will be considered successful for the ambulatory ECG component of 6-month effectiveness endpoint. Adjustments to all cardiovascular medications including antiarrhythmic drugs and dates of all DC Cardioversions will be captured on the case report forms.

Only those subjects that have a baseline and 6-month post-procedure 48-hour ambulatory ECG monitor data that are readable by the core lab or are missing ambulatory ECG data but were 6-month effectiveness failures based on other criteria at the time of the visit cutoff date will be included in the analysis of this

objective. Specifically, the denominator for the 6-month effectiveness rate will include all subjects that had at least one Phased RF ablation procedure where an investigational catheter was deployed into the left atrium and have baseline and 6-month ambulatory ECG monitor data available or do not have ambulatory ECG data available but were 6-month effectiveness failures based on other criteria. The numerator will include all subjects in the denominator that meet all four 6-month effectiveness conditions. A two-sided 95% exact confidence interval for 6-month effectiveness rate will be calculated.

12.3.1.5 Determination of subjects for analysis

Only those subjects that have completed both a baseline and 6-month 48 hour ambulatory ECG monitor or are 6-month effectiveness failures based on other criteria will be included in the main analysis cohort for this objective.

In the event that the recording duration of the ambulatory ECG monitor exceeds 48 hours (e.g. a 7 day ECG patch monitor is used), the AF burden will be computed by the core laboratory for the initial 48 hours only.

Likewise, in the event the ambulatory ECG monitor is less than 48 hours (e.g. due to inadequate ECG patch monitor fixation, subject compliance) the AF burden will be determined by the core laboratory based on the total usable or analyzable recording period. Subjects may be asked to repeat an ambulatory ECG monitoring session if less than 24 hours of analyzable monitoring time is obtained. Subjects with less than 24 hours of usable ambulatory ECG recording time will be considered missing in the analysis (unless they are 6-month effectiveness failures based on other criteria) and included in sensitivity analyses as described below.

12.3.1.6 Confidence Interval Width

The 6-month effectiveness rate among all 138 subjects randomized to the ablation management arm in TTOP-AF was 55.8% (77/138; 95% CI: 47.1% - 64.2%). However, in this intention-to-treat analysis, 17 subjects missing their 6-month ambulatory ECG monitor assessment were included in the analysis as failures. If only subjects with 6-month ambulatory ECG monitor data available in TTOP-AF were included in the analysis (the analogous analysis cohort in this study) the 6-month effectiveness rate was 63.6% (77/121; 95% CI: 54.4% - 72.2%). However, the TTOP-AF protocol required amiodarone be discontinued 28 days prior to the 6-month visit, did not require discontinuation of other antiarrhythmic drugs or DC cardioversions until 5 days prior to the 6-month ambulatory ECG monitor assessment. Thus, while it is expected that the estimated 6-month effectiveness rate in this study will be greater than 50%, it may be less than 64% due to differences in allowed concomitant therapy use between studies.

Based on the following assumptions:

- Up to 420 subjects will be enrolled
- 300 subjects are required to complete the 30-day post-ablation visit and have the opportunity for a reablation procedure (i.e. complete 6-month visit)

or complete the 30-day post-reablation visit if a reablation procedure is required
- Total of 55 study centers activated
- 14 months to activate the 55 centers
- Enrollment rate of 0.4 subjects per center per month once activated
- 30% of subjects will be re-ablated prior to their 6-month visit
- 10% annualized attrition rate

It was estimated via a simulation study that approximately 284 subjects would complete the 6-month ambulatory ECG monitor assessment. Assuming 200 subjects have evaluable baseline and 6-month ambulatory ECG monitor data and the observed 6-month effectiveness rate is 55%, then the exact 95% two-sided confidence interval should have a width no larger than 14.2% with a lower limit of at least 47.8%. Similarly, if the observed 6-month effectiveness rate is 50%, the confidence interval width should be no greater than 14.3% with a lower limit of at least 42.9%.

12.3.1.7 **Missing data**

Subjects will only be included in this analysis for the 6-month effectiveness objective if they have both a baseline and 6-month 48-hour ambulatory ECG monitor that are readable by the core lab or are missing a 48-hour ambulatory ECG monitor data and 6-month effectiveness failures based on other criteria at the time of the visit cutoff date. However, should the issue of missing data arise; all ablated subjects that complete the 6-month visit at the time of the visit cutoff regardless of ambulatory ECG monitor data status will be included in a tipping point analysis to evaluate the impact of missing data. Specifically, subjects completing the 6-month study visit but missing the ambulatory ECG monitor assessment who are not 6-month effectiveness failures based on other criteria will be included as successes and then iteratively included as failures in the tipping point analysis.

12.3.2 Secondary Objective #2: Acute procedural success

12.3.2.1 **Objective**

Confirm acute post-procedural effectiveness.

12.3.2.2 **Hypothesis**

There is no pre-specified hypothesis associated with this secondary objective.

12.3.2.3 **Definition acute procedural success**

Acute procedural success is defined as meeting all four of the following conditions:
1. Only Phased RF catheters used in the left atrium to achieve procedure success AND
2. All accessible pulmonary veins were isolated (entrance block)
3. CFAEs and high frequency intracardiac electrogram amplitudes were mapped and ablated as necessary with Phased RF System

4. Sinus rhythm is restored at the end of the ablation procedure (with or without cardioversion)

12.3.2.4 **Analysis Methods**

All ablation procedure parameters will be captured on the case report forms. For estimating the acute success rate, all subjects with an attempted ablation where at least one of the Phased RF catheters were deployed into the left atrium will be included in the denominator. The numerator will include all subjects in the denominator who met all the conditions for acute procedural success defined above. A two-sided lower 95% exact confidence interval for the acute procedural success rate will be calculated. Subjects that have a reablation attempt will be considered acutely successful if they meet all the conditions for their index procedure and conditions 1 and 4 of the acute success definition for their reablation attempt since the source of recurrent AF will be unknown.

In addition to calculating the acute success rate on a per subject basis, the acute success rate will be calculated on a per procedure basis. The denominator for the per procedure rate will be all Phased RF procedures where at least one Phased RF catheter was deployed into the left atrium. The numerator will be all Phased RF procedures in the denominator that meet all four conditions of the acute success definition. A two-sided 95% two-sided confidence interval for this rate will also be calculated using the method of Rao and Scott for clustered binary data since subjects may have up to two ablation procedures.

12.3.2.5 **Determination of subjects for analysis**

All ablation procedures that meet the cutoff date for the analysis of the primary objective where at least one Phased RF catheter was deployed into the left atrium will be included in the analysis.

12.3.2.6 **Missing data**

There is not expected to be any missing data associated with the analysis of this objective since the objective is evaluated at the time of the procedure.

12.3.3 Secondary Objective #3: Pulmonary Vein Stenosis

12.3.3.1 **Objective**

Characterize the incidence of PVS 3 months post ablation procedure as determined by MRI or CT scan.

12.3.3.2 **Hypothesis**

There is no pre-specified hypothesis associated with this secondary objective.

12.3.3.3 **Definition of pulmonary vein stenosis**

Pulmonary vein stenosis will be defined as: a greater than 70% reduction in the baseline luminal diameter.

12.3.3.4 **Analysis Methods**

One hundred (100) subjects will be randomized to the PVS assessment cohort. Subjects randomized to the PVS assessment cohort will have a CT-scan or MRI scan at their baseline visit and a CT-scan or MRI scan for PVS assessment at their first 3-month post-ablation visit (e.g. subjects with a reablation procedure following their 3-month post index ablation assessment will not have another scan at their 3-month post reablation visit). The core laboratory's assessment of PVS status will be collected on the CRFs. For computing the PVS rate at 3 months post ablation the denominator will be all subjects that are randomized to the PVS assessment cohort, have at least one ablation procedure with one or more Phased RF catheters deployed, and have evaluable CT or MRI scans available at their baseline and 3-month follow up visits. The numerator will be all subjects included in the denominator that were classified by the core laboratory as having PVS by the core laboratory. A two-sided 95% exact confidence interval for the 3-month post-procedure PVS rate will be calculated.

12.3.3.5 **Determination of subjects for analysis**

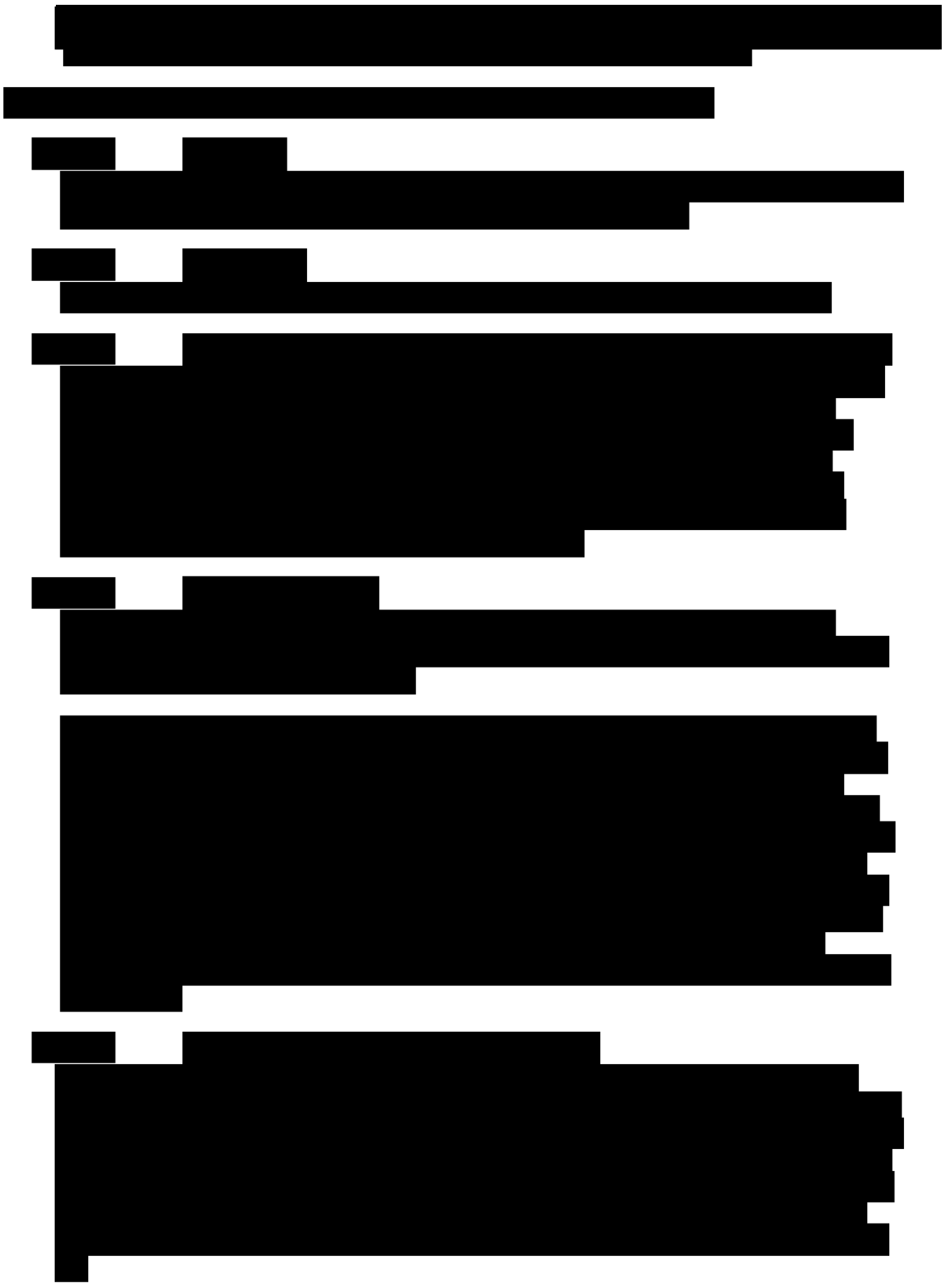
Only those subjects that are randomized to the PVS assessment cohort, have at least one ablation procedure with one or more Phased RF catheters deployed in the left atrium, and have CT or MRI scans at baseline and at the 3-month follow-up visit (or 3-month post-reablation visit if subject was reablated) that are readable by the core lab will be included in the analysis of this objective.

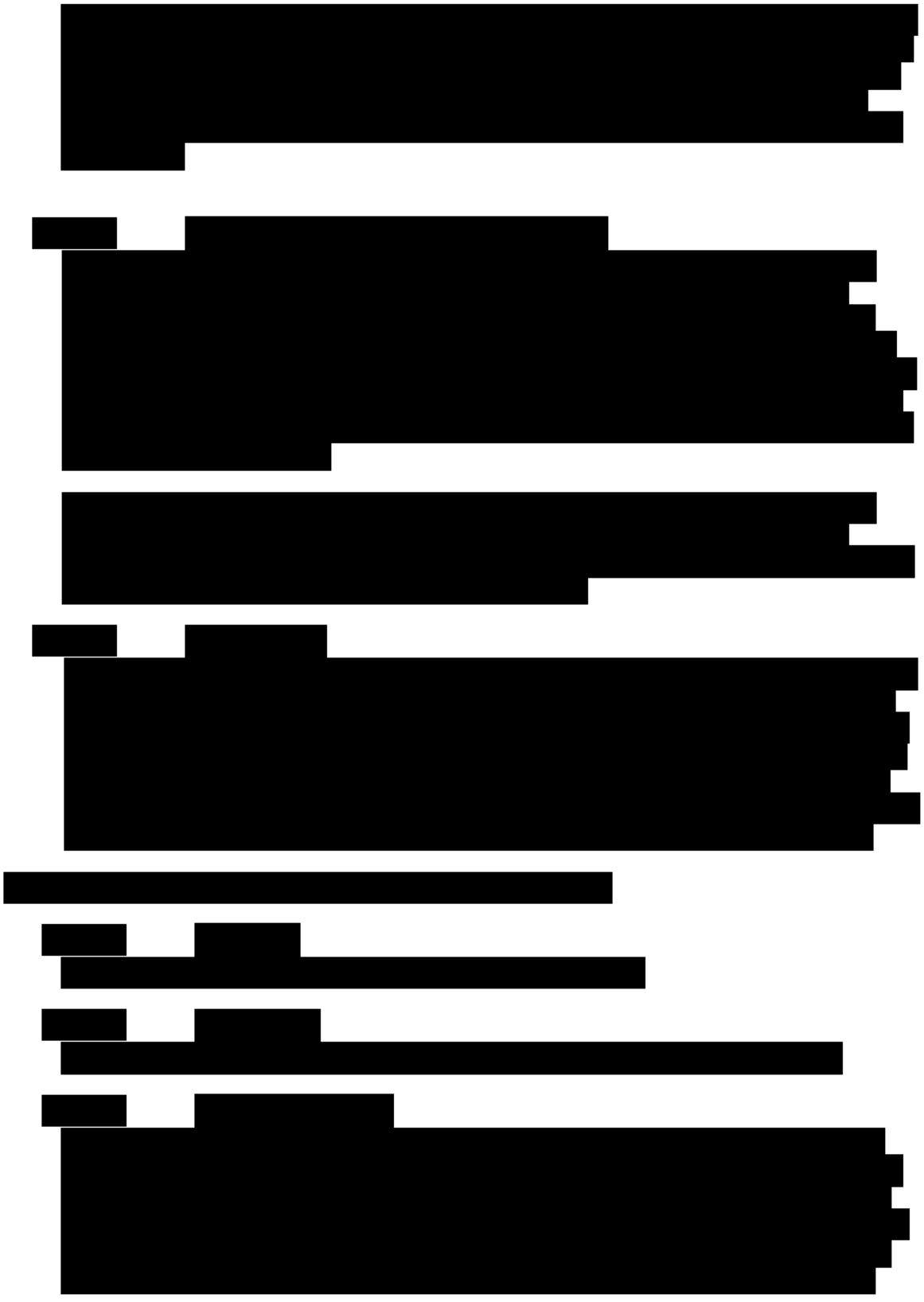
12.3.3.6 **Confidence Interval Width**

The PVS rate among all 176 ablated subjects in the TTOP-AF study was 4% (7/176; 95% CI: 1.6% to 8%). Based on the added training and other mitigation strategies employed in this protocol to avoid PVS it is assumed that the true PVS rate will be 2%. If at least 80 of the 100 subjects randomized to the PVS assessment cohort have readable baseline and 3-month follow-up MRI or CT-scans and the observed PVS rate is 2% the exact 95% two-sided confidence should have a width no larger than 7.8% with an upper confidence boundary no greater than 8%.

12.3.3.7 **Missing data**

Subjects missing both a readable baseline and 3-month follow-up MRI or CT-scan will not be included in the main analysis cohort for this objective. However, should the issue of missing data arise; all subjects randomized to the PVS assessment cohort with at least one Phased RF catheter deployed in the left atrium will be included in a tipping point analysis regardless of whether MRI or CT-scans are available. Specifically, subjects randomized to this cohort, but missing an evaluable 3-month MRI or CT-scan will be included as PVS negative and iteratively added as PVS positive in the tipping point analysis.





[redacted]

[redacted]

13. DATA AND QUALITY MANAGEMENT

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

The data reported on the CRFs shall be derived from source documents (Medical Records, Procedure Reports and/or Technical Support Forms) and be consistent with these source documents, and any discrepancies shall be explained in writing.

Generator files will be uploaded to secure servers.

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

Sponsor may form a Publication Committee to manage publications utilizing data from this study with the goal of publishing results.

14. WARRANTY/INSURANCE INFORMATION

14.1 Warranty

Warranty information is provided in the product packaging for the investigational system and additional copies are available upon request.

14.2 Insurance

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 MEC.

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

15. MONITORING

It is the responsibility of Medtronic to ensure proper monitoring of the study per regulations. Appropriately trained Medtronic personnel or delegates appointed by Medtronic will perform study monitoring at the study center in order to ensure that the study is conducted in accordance with the CIP, the signed Clinical Trial Agreement, and applicable regulatory requirements. Medtronic must therefore be allowed access to the subjects' clinic and hospital records when so requested as per the consent form, Privacy Authorization (US only) and Clinical Trial Agreement. Procedures required in this CIP require source documentation. A separate monitoring plan will detail levels of source document verification for this study.

15.1 Monitoring Visits

Monitoring visits will be conducted periodically to assess study progress, the investigator's adherence to the CIP, regulatory compliance including but not limited to IRB/MEC/HREC approval and review of the study, maintenance of records and reports, and review of source documents against subject case report forms. Monitors facilitate site regulatory and study compliance by identifying findings of non-compliance and communicating those findings along with recommendations for preventive/corrective actions to site personnel. Communication with the site personnel occurs during the visit and following the visit via a written follow-up letter. Monitors may work with study personnel to determine appropriate corrective action recommendations and to identify trends within the study or at a particular center.

Frequency of monitoring visits will occur based on subject enrollment, duration of the study, study compliance, findings from previous monitoring visits and any suspected inconsistency in data that requires investigation. The amount of subject data monitored against source documentation is determined by type of study and timing of data cutoff for study deadlines.

Storage and accountability of investigational product used for this study will be assessed.

15.2 Access to the Center and Study Materials

The investigator will permit study related monitoring, audits, IRB/MEC/HREC review and regulatory inspections by providing direct access to source data and source documents.

16. REQUIRED RECORDS AND REPORTS

16.1 Investigator records

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

during the 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 product approval or the date on which the investigation is terminated or the date that the records are no longer required for purposes of supporting a pre-market approval application.

- All correspondence between the IRB/MEC, sponsor, monitor, and/or the investigator that pertains to the investigation, including required reports.
- Subject's case history records, including:
  - Signed and dated informed consent form: In U.S., signed by subject. In EEA, signed by subject and investigator.
  - Observations of adverse events/adverse device effects
  - Medical history
  - Procedure and follow-up data
  - Documentation of the dates and rationale for any deviation from the protocol
- Electronically signed and dated CRFs.
- Device Disposition Logs containing Model numbers of devices delivered to the site, subject IDs of the subjects ablated, received dates of generators and catheters, used dates, returned-to-sponsor dates and reasons, initials of all persons who received, used or disposed each generator or catheter, and method of disposal/destruction.
- All approved versions of the Investigation Plan and Investigator Brochure/Report of Prior Investigations Summary
- Signed and dated Clinical Trial Agreement.
- Current curriculum vitae (signed and dated in Europe only) of principal investigators and key members of investigation site team
- Delegated task list.
- 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.
- Study training records for site staff.
- Insurance certificates as applicable
- Any other records that FDA and local regulatory agencies require to be maintained.
- Final Study Report including the statistical analysis.

16.2 Investigator reports

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

inspection and to the retention requirements as described above for investigator records.

Safety data investigator reporting requirements are listed in Section 10.7 of the Adverse Event section. The investigator shall prepare and submit in a complete, accurate and timely manner the reports listed in this section.

Table 15: Investigator reports applicable for all geographies per Medtronic requirements

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

Table 16: Investigator reports applicable to the United States per FDA regulations

Report	Submit to	Description/Constraints
Withdrawal of IRB/MEC approval (either suspension or termination)	Sponsor	The investigator must report a withdrawal of approval by the reviewing IRB/MEC of the investigator's part of the investigation within 5 working days. *(21 CFR 812.150(a)(2))*
Progress report	Sponsor and Ethics Board	The investigator must submit this report to the sponsor and IRB/MEC at regular intervals, but in no event less than yearly. *(21 CFR 812.150 (3))*.
Study deviations	Sponsor and Ethics Board	Notice of deviations from the CIP to protect the life or physical well-being of a subject in an emergency shall be given as soon as possible, but no later than 5 working days after the emergency occurred. Except in such emergency, prior approval is required for changes in the plan or deviations. If the deviation may affect the scientific soundness of the plan or the rights, safety and welfare of the subjects, the deviation must be approved by Medtronic, the IRB/MEC, and the FDA/applicable regulatory authorities. If the deviation does not affect these issues then only Medtronic must approve it. *(21 CFR 812.150(a)(4))*
Failure to obtain informed consent prior to investigational device use	Sponsor and Ethics Board	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 Ethics Board 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	Ethics Board 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 17: Investigator reports applicable to Europe per ISO 14155

Report	Submit to	Description/Constraints
Withdrawal of IRB/MEC approval	Sponsor	Report if required by local law.
Progress Report	Sponsor and Ethics Board	Provide if required by local law or IRB/MEC.
Study Deviations	Sponsor and Ethics Board	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. 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 Ethics Board	Informed consent shall be obtained in writing and documented before a subject is enrolled into the clinical investigation. *(ISO 14155:2011)*

Table 18: Investigator Reports Applicable to Canada

Report	Submit To	Description/Constraints
Withdrawal of Ethics Board approval	Sponsor	The investigator must report a withdrawal of approval by the reviewing Ethics Board of the investigator's part of the investigation within 5 working days. (Medtronic Requirement)
Study Deviations	Sponsor and Ethics Board	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. (Medtronic Requirement)
Failure of a device	Sponsor and Health Canada	In the event of an incident that is related to a failure of the device or a deterioration in its effectiveness, or any inadequacy in its labeling or in its directions for use and 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 the incident and the circumstances surrounding it to the Director and the manufacturer or importer of the device within 72 hours. After its discovery. (Canada Medical Devices Regulations, SOR/98-282; 77, 59).
Final Report	Ethics Board Relevant Authorities	This report must be submitted within 3 months of study completion and/or termination of the investigation or investigator's part of the investigation (Medtronic Requirement)

In addition, if an Ethics Board takes any action with respect to this clinical study, copies of all pertinent documentation must be forwarded to the sponsor in a timely manner.

16.3 Sponsor records

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

- All correspondence which pertains to the investigation
- Investigational device Traceability record containing Model numbers of devices, shipping date and name and address of person that received shipped device, Location (if different than person shipped to), transfer and receipt by Medtronic dates. (All Geographies)
- Signed Investigator Trial Agreements, financial disclosure and current signed and dated (Europe only) curriculum vitae of principal investigator and key members of the investigation site team, delegated task list
- All signed and dated case report forms submitted by investigator, including reports of AEs, ADEs and Device Deficiencies, and CRF corrections
- Samples of informed consents, 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 investigation will be conducted
- Correspondence with authorities as required by national legislation
- Insurance certificates (Europe only)
- Forms for reporting any adverse events and adverse device effects
- Names/contact addresses of monitors
- Statistical analyses and underlying supporting data
- Final report of the clinical investigation
- The Clinical Investigation Plan, Investigator Brochure/Report of Prior Investigations summary and study related reports, and revisions
- Study training records for site personnel and Medtronic personnel involved in the study
- Forms for reporting any adverse events, adverse device effects and device deficiencies.
- Any other records that local regulatory agencies require to be maintained.

16.4 Sponsor reports

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

investigation. Safety data Medtronic reporting requirements are listed in section 10 of the Adverse Event section.

Table 19: Sponsor reports for Europe

Report	Submit to	Description/Constraints
Premature termination or suspension of the clinical investigation	Investigators Ethics Board Relevant authorities	Provide prompt notification of termination or suspension and reason(s). *(ISO 14155:2011)*
Withdrawal of IRB/MEC approval	Investigators, Ethics Board Relevant Authorities	Investigators, IRBs/MECs will be notified only if required by local laws or by the IRB/MEC.
Withdrawal of CA approval	Investigators Ethics Board and relevant authorities	Investigators, IRBs/MECs will be notified only if required by local laws or by the IRB/MEC.
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	Ethics Board, Regulatory Authorities (upon request)	This will be submitted to the IRB/MEC only if required by the IRB//MEC).
Final report	EEA Investigators, Ethics Boards, Regulatory authorities upon request	The investigator shall have the opportunity to review and comment on the final report. If a clinical investigator does not agree with the final report, his/her comments shall be communicated to the other investigator(s). The principal clinical investigator in each center shall sign the report. *(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)* Site specific study deviations will be submitted to investigators approximately annually.
Vigilance Reporting	Competent Authorities	Report incidents and near-incidents within 10 (incidents) or 30 (near-incidents) days. (Meddev.2.12-1 rev 5)
Significant new information	Ethics Board and Regulatory Authorities	Ensure that the Ethics Boards and Regulatory Authorities are informed of significant new information about the clinical investigation (ISO 14155:2011)

Table 20: Sponsor reports for the United States

Report	Submit to	Description/Constraints
Premature termination or suspension of the clinical investigation	Investigators Ethics Boards, Relevant authorities	Provide prompt notification of termination or suspension and reason(s). *(ISO 14155-1:2003(E)(k)),(MHLW Ordinance 36, Article 32)*
Unanticipated Adverse Device Event	Investigators, Ethics Board, FDA, and relevant authorities	Notification within ten working days after the sponsor first receives notice of the effect. *(21 CFR 812.150(b)(1))*
Withdrawal of Ethics Boards, approval	Investigators, IRB/MEC, FDA, and relevant authorities	Notification within five working days. *(21 CFR 812.150(b)(2))*
Withdrawal of FDA approval	Investigators, Ethics Boards, 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	Ethics Boards, FDA	Progress reports will be submitted at least annually. *(21 CFR 812.150(b)(4)(5), 812.36(f)*
Recall and device disposition	Investigators Ethics Boards, relevant authorities FDA	Notification within 30 working days and will include the reasons for any request that an investigator return, repair, or otherwise dispose of any devices. *(21 CFR 812.150(b)(6))*
Failure to obtain informed consent	FDA	Investigator's report will be submitted to FDA within five working days of notification. *(21 CFR 812.150(b)(8))*
Final report	Investigators, Ethics Boards, Regulatory authorities upon request, and FDA	Medtronic will notify FDA within 30 working days of the completion or termination of the investigation. A final report will be submitted to the FDA, investigators, and IRBs/MECs within six months after completion or termination of this study. *(21 CFR 812.150(b)(7))*
Study deviation	Investigators	Ensure that all deviations from the Clinical Investigation Plan are reviewed with the appropriate clinical investigator(s), are reported on the case report forms and the final report of the clinical investigation. (ISO 14155:2011) Site specific study deviations will be submitted to investigators approximately annually.

Table 21: Sponsor reports for Canada

Report	Submit to	Description/Constraints
Premature termination or suspension of the clinical investigation	Investigators, Ethics Board Relevant authorities	Provide prompt notification of termination or suspension and reason(s). *(ISO 14155:2011)*
Recall and device disposition	Investigators, Head of Institution, Ethics Board, Regulatory Authorities, FDA	Notification within 30 working days and will include the reasons for any request that an investigator return, repair, or otherwise dispose of any devices. *(Medical Devices Regulation Mandatory Problem Reporting 63 – 65.1.)*
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)* Site specific study deviations will be submitted to investigators approximately annually.
Vigilance reporting	Health Canada	If a product complaint occurring in Canada meets the criteria of Mandatory Problem Reporting for Medical Devices

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

[redacted]

[redacted]

[redacted]

[redacted]