Symplicity AF Clinical Investigation Plan

Version 18.0

19Aug2020

NCT02064764

Symplicity AF

Clinical Investigation Plan

Version 18

19AUG2020

Regional Sponsors and Contacts
United States Medtronic, Inc. 8200 Coral Sea Street NE Mounds View, MN U.S.A. 55112 1-800-328-2518 Europe, Middle East, Africa Medtronic, Bakken Research Center B.V. Endepolsdomein 5 6229 GW Maastricht The Netherlands (+31)-43-35-66-566

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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 Clinical study leader Marina Ostanniy, Pr. Clinical Research Specialist Direct Phone: +17635269751 marina.ostanniy@medtronic.com	*Europe, Middle East, Africa (EMEA)* Anita van Wijlick MSc, Sr. Clinical Research Specialist Direct Phone: +31 (0)6 22592645 anita.wijlick@medtronic.com
Monitoring contact	
Worldwide Monitoring leader Beth A. Ornell, MS, Clinical Monitoring Manager Direct Phone: +1 763-280-2332 beth.a.ornell@medtronic.com	

CORE LABS

Table 2: Study Core Labs

Core Lab	**Contact information**	**Purpose**
VasCore	One Bowdoin Square 10th Floor Boston, MA 02114 Phone: 617-726-5552	Assessment of Renal Duplex Ultrasound (RDUS)
Beth Israel Deaconess Medical Center	375 Longwood Avenue, 3rd Floor Boston, MA 02215 Phone: 617-667-7000	Assessment of renal angiogram for renal stenosis
Intelemage/ Medidata	700 W. Pete Rose Way Cincinnati, OH 45203 Phone: 973-659-6780	Study specific image uploading and viewing platform

COMMITTEES

Table 3: Committee contact information

Committee Member	Contact information	Purpose
Steering Committee Larry Chinitz, MD Principal Investigator	New York University, Langone Medical Center 333 East 30th Street New York, NY 10016	Provide consultation on therapy and product usage throughout the lifecycle of the clinical study.
Clinical Events Committee (CEC)	Provided under separate cover, if requested.	Provide unbiased review of adverse events and adjudicate all death and endpoint events.
Data Monitoring Committee (DMC)	Provided under separate cover, if requested.	Provide unbiased review of safety data and provide recommendations for study continuation or termination.

1. INTRODUCTION

1.1 Study purpose

Medtronic, Inc. is sponsoring the Symplicity AF study, a prospective, randomized, multi-center clinical study. This is an investigational, feasibility study in the United States; the study is a post-market interventional study in Europe. The purpose of this clinical study is to evaluate the feasibility of performing both renal artery denervation and pulmonary vein isolation on the same patient with the intent of characterizing both safety and effectiveness in a paroxysmal and persistent atrial fibrillation (AF) population with hypertension. To assess safety, a primary objective will measure the occurrence of a composite safety endpoint and, to assess effectiveness, a primary objective will measure freedom of chronic treatment failure through a minimum of six months of follow-up. The Arctic Front Advance™ Cardiac Cryoablation system and Symplicity™ Spyral Renal Denervation system (Symplicity Spyral™ Multi-Electrode Renal Denervation Catheter and the Symplicity G3™ Renal Denervation RF Generator, hereafter referred to as the Symplicity Spyral Catheter and Symplicity G3 Generator) will be used in the study. Both are commercially available in Europe. The Arctic Front Advance Cardiac Cryoablation system is commercially available in the United States; however, is not approved for the treatment of persistent AF with an AF episode duration of6 months and longer; therefore, it is considered investigational in this specific persistent AF patient population. The components of the Symplicity Spyral Renal Denervation System are investigational in the United States.

This study has been designed to support the following proposed Indication for Use should Medtronic choose to study this further:

Renal denervation with the Symplicity System increases the success rate and augments the benefits of pulmonary vein isolation with the Arctic Front Advance System in patients with symptomatic drug refractory paroxysmal and persistent AF and uncontrolled hypertension for the prevention of AF recurrence.

1.2 Study description

The study is expected to be conducted at up to 12 centers located in The United States and up to three centers in Europe. Up to 245 subjects will be enrolled in the study to ensure there are 70 randomized subjects. The number of enrollments permitted relative to the number of subjects to be randomized is high since it is expected that a fair number of subjects will not meet all screening criteria (rigorous blood pressure monitoring and renal anatomy) once consented. Center randomization will be capped at 50% (35) of the total randomized subjects.

Randomized study subjects will be followed for a minimum of six months, and then every six months thereafter until official study closure as determined by Medtronic and/or regulatory authority, whichever occurs first. Accordingly, the expected total study duration is approximately fifty-seven months, representing approximately fifty-one months of enrollment and six months of subject follow-up after the last patient has undergone the study procedure.

Interim analyses of the primary effectiveness objective will take place and if data are deemed to sufficiently characterize this study objective by the sponsor

at one of these analyses, enrollment may be stopped.

2. BACKGROUND AND JUSTIFICATION

Hypertension[1] and AF[2] share many commonalities in demographics, prevalence, and disease implications. These two diseases often co-exist and are each responsible for considerable deleterious changes in morbidity and mortality.[3] By relative risk score evaluation, the risk of developing AF in hypertensive patients is modest (relative risk score = 1.4 to 2.1) when compared to other more serious cardiac conditions, such as heart failure (relative risk score = 6.1 to 17.5) and valvular heart disease (relative risk score = 2.2 to 8.3).[4] Yet, due to the much higher prevalence of hypertension in the general population, hypertension accounts for more actual cases of AF than compared to any other risk factor.[5] Approximately 25% of the United States population has high blood pressure[1], which makes it the primary risk factor for AF development in North America.[3,6] Currently hypertension is the most prevalent and independent risk factor for developing AF, but it also is potentially the most modifiable risk factor for halting the development of AF.[2,7]

On its own hypertension is associated with several long-term maladaptive cardiac adjustments, including: left ventricular cardiac hypertrophy, left atrial enlargement, slowing of left and right atrial conduction velocity, and impaired ventricular filling.[4] Nonetheless, these structural and physiological changes in the hypertensive heart also predispose and start the cardiac abnormalities which also help to initiate AF. This link between hypertension and AF is seen with demographic incidence rates. The annual incidence of AF is approximately 19.2 per 1,000 person-years;[7] however, when examined in the subset of preexisting hypertensive patients, the incidence of AF is about 94 per 1,000 person-years.[8] Follow-up cohort studies demonstrated that hypertension was present in approximately 50% of all North American patients with AF[3,6] and that hypertension was shown to be causative to AF in about 15% of the patients.[2]

Recently, a series of studies have demonstrated that pharmaceutical therapies guided at reducing hypertension have also reduced atrial fibrillation incidence in patients with hypertension, heart failure, and myocardial infarction. In particular, pharmaceutical blockage of the renin-angiotensin system (by either angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor antagonists) proved to be the most effective in reducing the incidence of AF.[9,10,11,12] Animal studies confirmed that the duration of AF was decreased when treated with ACE inhibitors and concluded that the renin-angiotensin pathway played a critical role in arrhythmogenic atrial remodeling.[13] More recently, therapeutic renal denervation, which is the deliberate disruption of the nerves connecting the kidneys with the central nervous system, has been shown to be an effective means of reducing elevated sympathetic nervous system (SNS) activity, which is a common and key factor in disease states such as hypertension, heart failure and atrial fibrillation. Renal denervation modulates the SNS activity by 1) reducing the sympathetic control of renal function (renin release, sodium excretion and renal blood flow) and 2) removing the renal afferent sympathetic contribution to central blood pressure elevation.

Renal denervation was developed as a potential treatment for hypertension based on prior surgical studies demonstrating reduction in blood pressure with surgical disruption of thoracoabdominal sympathetic nerves and surgical nephrectomy in renal failure patients. Renal denervation is believed to interrupt efferent sympathetic nerves

impacting renal function as well as afferent nerves impacting feedback to the brain and thus systemic sympathetic tone. A series of early feasibility clinical studies demonstrated impact on hypertension as well as other associated disease processes where increased systemic sympathetic tone is believed to be involved, such as heart failure, renal dysfunction, diabetes, and cardiac arrhythmias. Following the SYMPLICITY HTN-3 study, which raised concerns about incomplete denervation with the Symplicity renal denervation system and lack of adequate control in some prior studies, two recent feasibility studies of renal denervation using the Symplicity Spyral renal denervation system and catheter have successfully addressed these issues and demonstrated the ability of this system to reduce blood pressure both in the absence and in the presence of antihypertensive drugs. Each of these studies reported on 80 subjects with combined systolic and diastolic hypertension (office systolic blood pressure between 150 and less than 180 mmHg; diastolic office pressure of 90 mmHg or above, and 24-hour mean systolic pressure between 140 and less than 170 mmHg). The OFF-MED study enrolled subjects who had either not been treated with antihypertensive drugs or had these drugs discontinued for a period of time before randomization. The ON-MED study enrolled subjects prescribed 1, 2, or 3, antihypertensive medications.

The SPYRAL OFF-MED study[14] demonstrated 3-month reductions in both office systolic blood pressure reduction (-7.7-mm Hg; *P* = .016) and mean 24-hour systolic pressure (-5.5 mmHg (p=0.04). There were no major safety events in either arm. Significant reductions were also observed between groups for multiple parameters including office diastolic blood pressure and 24-hr mean diastolic blood pressure. This trial provided biological proof of principle for the efficacy of catheter-based renal denervation to reduce blood pressure in patients with hypertension not treated with antihypertensive medications, addressing the limitations identified from the prior SYMPLICITY HTN-3 study.

The SPYRAL ON-MED study[15] demonstrated 6-month placebo subtracted reductions in both office systolic pressure (-6.8 mmHg; p=0.02) and mean 24-hour systolic pressure (-7.4; -p=0.005) in the presence of commonly used antihypertensive medications. Significant reductions were also observed between groups for multiple parameters including office diastolic blood pressure, 24-hr mean diastolic blood pressure, daytime systolic blood pressure and nighttime systolic blood pressure. Examination of the circadian 24-hr blood pressure normalized to waking time indicated that blood pressure reductions were consistent throughout the day and night including the high-risk “morning surge” period. Thus, the effects of renal denervation may provide additional clinical benefit during the high-risk period unlike drug therapy. The extent of blood pressure reduction grew during follow up, raising the possibility that further reduction may be seen with more prolonged follow-up. No major adverse events out to 6 months were reported.

In order to test the hypothesis in the SPYRAL PIVOTAL - SPYRAL HTN-OFF MED study that renal denervation decreases blood pressure and is safe when studied in the absence of antihypertensive medications, study subjects were randomized to the Denervation or Control group in a 1:1 fashion. In addition to subjects being blinded to their randomization assignment, site personnel involved in the measurement of office blood pressure were also blinded to study subjects’ randomization assignment through the primary endpoint to prevent potential bias of results. Subjects were studied in the absence of antihypertensive medications to assess the impact of renal denervation on

systolic blood pressure in the absence of medication.

Study enrollment was stopped for efficacy after the first interim analysis in February 2020. Data from the initial 80 patients with 3 months follow up from the SPYRAL HTN-OFF MED study was combined with data from the initial 251 patients with 3 months follow up from the SPYRAL PIVOTAL-SPYRAL HTN-OFF MED study and was presented at ACC World Congress of Cardiology in March 2020. Concurrently, an article presenting the data was published in the Lancet. A brief summary of the SPYRAL PIVOTAL-SPYRAL HTN-OFF MED data is provided below.

The primary endpoint, change in 24-h blood pressure at 3 months, was compared between groups. Drug surveillance was done to ensure patient compliance with absence of antihypertensive medication. The primary analysis was done in the intention-to-treat population. Safety events were assessed to 3 months.

From June 25, 2015, to Oct 15, 2019, 1519 patients were enrolled, of whom 1188 were excluded because they did not meet inclusion criteria. 166 were randomly assigned to renal denervation and 165 to the sham procedure (80 were included in the pilot and 251 in Pivotal).

There were no major safety events reported at 1 month. There was one major safety event in each treatment group up to 3 months (one admission to hospital for hypertensive crisis or emergency in the renal denervation group and one new stroke in the sham procedure group), and neither was attributed to the device or trial procedures.

For the primary efficacy endpoint of changes from baseline in 24-h systolic blood pressure at 3 months, there was a significant difference between the renal denervation and sham procedure groups. This endpoint was met with a posterior probability of superiority greater than 0.999 and a treatment difference of -3.9 mm Hg (95% BCI -6.2 to -1.6)**.** For the secondary efficacy endpoint of difference in 3-month changes in office systolic blood pressure between the two groups, the difference was significant and the endpoint was met (difference -6.5 mm Hg (95% BCI -9.6 to -3.5), with posterior probability of superiority of more than 0.999**.** The blood pressure changes analysed using the prespecified ANCOVA-adjusted frequentist analysis of the overall population show similar changes in blood pressure to Bayesian results.

A small pilot study in hypertensive patients with paroxysmal and persistent AF demonstrated the benefits of concomitant AF ablation and renal denervation (RDN) ablation.[16] When patients were given both simultaneous AF and RDN ablation, 69% of the subjects were AF-free at twelve-month post-ablation follow-up examination. This was compared to 29% of subjects that remained AF-free during the same study when they were only administered an AF ablation. The 40% difference in success rate was attributed to the differential success that is achieved when hypertension is controlled through sympathetic modulation and no longer adversely contributing to the disease progression of AF; in addition, direct effects on the atria following renal denervation are possible.

Until very recently, the treatment of AF had been focused on maintenance and regulation of rate, rhythm, and anti-coagulation. The current therapies largely ignore the underlying disease process including the sympathetic nervous system's involvement into the development of hypertension and structural heart disease which

can lead to the development of AF through atrial remodeling and subsequent maladaptive changes in atrial electrical conduction. Aggressive treatment of hypertension may reverse structural heart changes, reduce thromboembolic events, and retard/prevent AF. Patients with both paroxysmal and persistent AF are included in this study to better understand the treatment effect of renal artery denervation in combination with cryoablation along the AF disease continuum. In addition, this study will gather feasibility outcomes data on the use of the Arctic Front Advance and Arctic Front Advance Pro Cardiac Cryoablation Catheter for pulmonary vein isolation in the persistent AF population. In June 2020, FDA granted approval of Arctic Front Advance, Arctic Front Pro and Freezor MAX with the Persistent AF expanded indication for the treatment of drug refractory recurrent symptomatic paroxysmal and persistent atrial fibrillation (episode duration less than 6 months).

3. SYSTEM DESCRIPTION AND INTENDED USE

The study will be conducted using the components described in the table below (and future commercially released generations). Instructions for use of the devices used in this study are provided in their respective manuals. In Europe, centers will utilize the commercially available Symplicity Spyral Renal Denervation System, Arctic Front Advance Cardiac Cryoablation System and Reveal LINQ™ Insertable Cardiac Monitor System within intended use.

Table 4: System component information

Component	Model Number	Investigational / Market-released	Manufacturer
Symplicity Spyral™ multi-electrode renal denervation catheter (Symplicity Spyral™ catheter) and Symplicity G3™ renal denervation RF Generator (Symplicity G3™ generator)	IDERDN016 or IDEHTNRDN016 (Symplicity Spyral catheter) IDERDN017 or IDEHTNRDN017 (Symplicity G3 generator)	US: Investigational	Medtronic, Inc.
	RDN016 (Symplicity Spyral catheter) RDN017 (Symplicity G3 generator)	Europe: Market-released	
Arctic Front Advance Cardiac Cryoablation System	2AF234	US: Market-released for treatment of paroxysmal AF and persistent AF with an episode duration less than 6 months. Investigational for treatment of persistent AF with an episode duration over 6 months US: Investigational for treatment of persistent AF with an AF episode duration 6 months or greater.	Medtronic CryoCath LP
	2AF284		
	AFAPRO23		
	AFAPRO28		

	2AF233	Europe: Market-released	
	2AF283		
	AFAPRO23		
	AFAPRO28		
Reveal LINQ™ Insertable Cardiac Monitor (ICM) System	LNQ11 (Reveal LINQ ICM, Incision/Insertion Tool) 2090 (Medtronic Programmer) 9538 or PA96000 (Patient Assistant) 24950/24951/24952 (MyCareLink Patient Monitor)	US: Market-released Europe: Market-released	Medtronic, Inc.

3.1 Symplicity Spyral Renal Denervation System

The system consists of the following:

- Symplicity Spyral™ Multi-Electrode Renal Denervation Catheter
- Symplicity G3™ Renal Denervation RF Generator
- Symplicity RF Generator Component, Foot Switch
- Symplicity RF Generator Component, Power Cord

The Symplicity Spyral Renal Denervation System is intended for use of delivering low-level radiofrequency (RF) energy through the wall of the renal artery to denervate the human kidney.

In Europe, the commercially available product is indicated for the treatment of uncontrolled hypertension.

This system will be considered investigational in the United States for the duration of the clinical study.Arctic Front Advance Cardiac Cryoablation System

The system consists of the following:

- Arctic Front Advance Cardiac Cryoablation Catheter in two balloon sizes (23mm and 28mm)
- Arctic Front Advance Pro Cardiac Cryoablation Catheter
- Manual Retraction Kit
- The Freezor® *MAX* Cardiac Cryoablation Catheter in two curves (55mm and 66mm)
- Medtronic CryoCath® CryoConsole

Approved indication in the US: The Arctic Front Advance/Arctic Front Advance Pro Cardiac Cryoablation Catheters are indicated for the treatment of drug refractory recurrent symptomatic paroxysmal atrial fibrillation or persistent AF with an AF episode duration less than 6 months.

Approved indication in Europe: The Arctic Front Advance/Arctic Front Advance Pro Cardiac Cryoablation Catheters are indicated for the treatment of patients with atrial fibrillation.

Approved indication in the US: The Freezor *MAX* Cardiac Cryoablation Catheter is used as an adjunctive device in the endocardial treatment of paroxysmal atrial

fibrillation in conjunction with Arctic Front Advance/Arctic Front Advance Pro Cardiac Cryoablation Catheter for the following uses:

- gap cryoablation to complete electrical isolation of the pulmonary veins
- cryoablation of focal trigger sites, and
- creation of atrial flutter line between the inferior vena cava and the tricuspid valve

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

This system is considered investigational for use in the persistent AF population with an episode duration over 6 months in the United States.

3.2 Reveal LINQ ICM System

The system consists of the following:

- Reveal LINQ ICM
- Incision Tool
- Insertion Tool
- Medtronic CareLink Model 2090 programmer or CareLink Encore Model 22901 programmer
- MyCareLink® Home Monitor
- Reveal Patient Assistant

Approved indication in the US: The Reveal LINQ ICM is an implantable patient-activated and automatically-activated monitoring system that records subcutaneous ECG and is indicated in the following cases:

- Patients with clinical syndromes or situations at increased risk of cardiac arrhythmias
- Patients who experience transient symptoms such as dizziness, palpitation, syncope, and chest pain that may suggest a cardiac arrhythmia

Approved indication in Europe: The Reveal LINQ Insertable Cardiac Monitor is an implantable patient-activated and automatically-activated monitoring system that records subcutaneous ECG and is indicated in the following cases:

- Patients with clinical syndromes or situations at increased risk of cardiac arrhythmias
- Patients who experience transient symptoms that may suggest a cardiac arrhythmia

This device will be used to identify recurrent AF which is further described in Section 12: Statistical methods and data analysis.

The AF detection algorithm looks at incoherence patterns in a series of RR intervals over a period of 2 minutes to detect AF.

3.3 Additional system components

Additional components that may be used include Medtronic FlexCath™ sheaths and Medtronic Achieve™ and Achieve Advance™ mapping catheters. Medtronic may incorporate additional components into this clinical study as they receive appropriate license or regulatory approval and are released commercially by Medtronic.

4. REGULATORY COMPLIANCE

The Symplicity AF clinical study is an Investigational Device Exemption (IDE) study in the United States and a post-market interventional study in Europe. This clinical study is required to be in compliance with the CIP, Clinical Trial Agreement (CTA) and applicable regulations.

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

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

Ultimately, all centers in all geographies will follow and comply with:

- Principles of Declaration of Helsinki (including privacy and data protection laws), or the laws and regulations of each participating country, whichever affords greater protection for the study subjects
- 21 CFR Part 11 (Electronic Records, Electronic Signatures)
- 21 CFR Part 54 (Financial Disclosure by Clinical Investigators)
- The procedures described with in this CIP
- Local Ethics Board requirements

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

- In the United States, US FDA 21 CFR Parts
    - 50: Protection of Human subjects
    - 56: Institutional Review Boards
    - 812: Investigational Device Exemptions
- In Europe, Declaration of Helsinki 2013 and the local laws

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

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

Approval of the CIP, CIP revisions or CIP amendments is required from the following groups prior to any study procedures at a study center: Medtronic, FDA, regulatory body, Principal Investigators (where required by law), and an IRB/MEC at each study center.

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

5. METHODOLOGY

5.1 Study objectives

There are two primary objectives, one secondary objective, and six ancillary objectives for this study. The primary safety objective compares the rate of safety composite events between subjects randomized to receive both pulmonary vein isolation and renal artery denervation within one procedure compared to subjects randomized to receive pulmonary vein isolation alone. The primary effectiveness objective compares the proportion of subjects in each study arm that are free from a chronic treatment failure through all follow-up. Further details about study objectives can be found in Section 12.

5.2 Subject selection criteria

Subjects will be screened to ensure they meet all the inclusion and none of the exclusion criteria. IRB/MEC and Medtronic approval of the Symplicity AF CIP and Informed Consent Form must be obtained prior to enrolling subjects in the study.

Enrollment of the subject must occur prior to any study procedures take place.

5.2.1 Inclusion criteria

- Drug refractory recurrent symptomatic paroxysmal or persistent atrial fibrillation
    - Drug refractory is defined as: failed (drug is ineffective, or patient is intolerant) at least one Class I or III anti-arrhythmic drug
    - If the subject has persistent atrial fibrillation it must have been diagnosed within the last two years from the date of consent with a left atrial volume index ≤ 40 ml/m^2 within the last year from the date of consent
- Office-based systolic blood pressure > 140 mm Hg based on average of three blood pressure readings despite treatment with 1 or more antihypertensive medication(s). The subject should be on a stable antihypertensive drug regimen with no changes for a minimum of 2 weeks prior to enrollment and the antihypertensive drug regimen is not expected to change for at least 6 months, as determined by the subject's referring cardiologist and/or the investigator.
- Age 18 years to 80 years old
- Willing to give informed consent and agree to all study procedures, and is competent and willing to provide written, informed consent to participate in this clinical study
- Willing and able to be remotely monitored through the Medtronic CareLink® Network

5.2.2 Exclusion criteria

- Active systemic infection
- Cryoglobulinemia
- One or more pulmonary vein stents
- Type I Diabetes
- NYHA Class IV heart failure with in the past 6 months
- Renal artery anatomy that is ineligible for treatment including:
    - Lacks at least one renal artery for each kidney with ≥3 mm and ≤ 8 mm diameter and minimum treatable length per the Spyral Instructions for Use prior to a significant arterial branch *(NOTE: All renal arteries with ≥3 mm and ≤ 8 mm diameter with minimum treatable length per the Spyral Instructions for Use shall be treated, including dual renal arteries meeting these morphologic criteria.)*
    - Renal artery stenosis (>50%) or renal artery aneurysm in either renal artery
    - A history of prior renal artery intervention including balloon angioplasty or stenting
    - Renal artery which contain calcification which does not allow at least four radio frequency ablations to be delivered
    - Diffuse fibromuscular dysplasia (FMD) or FMD which does not allow at least four radio frequency ablations to be delivered; FMD defined as visible beading of the artery on angiography
    - Unilateral kidney
- Estimated Glomerular Filtration Rate (eGFR) of <30 mL/min/1.73m^2
- Primary pulmonary hypertension
- Pheochromocytoma, Cushing's Disease, coarctation of the aorta, untreated hyperthyroidism, primary hyperparathyroidism or hyperaldosteronism (Note: treated hyperthyroidism is permissible)
- Myocardial infarction, unstable angina pectoris, syncope, PCI/PTCA, or coronary artery stenting within 3 months prior to signing the consent form, or has widespread atherosclerosis with documented intravascular thrombosis or unstable plaques
- Cerebrovascular accident or TIA within 1 month prior to signing the consent form
- Prior ablation for atrial fibrillation in the left atrium
- Presence of a permanent pacemaker, biventricular pacemaker, atrial defibrillator or any type of implantable cardiac defibrillator (with or without biventricular pacing function)
- Cardiac valve stenosis for which a significant reduction of blood pressure is contraindicated
- A condition that would prohibit or interfere with ability to obtain an accurate blood pressure measurement using the protocol-specified automatic blood pressure monitor (e.g., arm diameter too large for the cuff)
- Serious medical condition, which may adversely affect the safety and/or effectiveness of the participant or the trial (e.g., patients with clinically significant peripheral vascular disease, abdominal aortic aneurysm, bleeding disorders such as thrombocytopenia, hemophilia, or significant anemia)

- Pregnant, nursing or planning to be pregnant. [Female participants of childbearing potential must have a negative serum or urine human chorionic gonadotropin (hCG) pregnancy test prior to angiography]
- Known history of drug use or alcohol dependency, lacks the ability to comprehend or follow instructions, or would be unlikely or unable to comply with study follow-up requirements
- Previous organ transplant
- Currently enrolled or plans to participate in a potentially confounding drug or device trial during the course of this study. Co-enrollment in concurrent studies is allowed when documented pre-approval is obtained from the Medtronic study manager.

5.3 Minimization of bias

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

- Subjects will undergo a rigorous screening to confirm eligibility for enrollment with defined inclusion/exclusion criteria prior to enrollment
- All centers will use the same version of the CIP and Case Report Form (CRFs)
- Data collection requirements and study procedures will be standardized for all centers
    - All investigational center personnel and Medtronic personnel will be trained on their respective aspects of the study using standardized training materials
    - All investigational center personnel will be trained on and required to follow the CIP
    - An independent CEC will be utilized to regularly review and adjudicate reported adverse events and deaths
    - An independent DMC will be utilized to 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 study have been considered and minimized by careful study design.

6. STUDY PROCEDURES

6.1 Investigator/center selection criteria

An Investigator/center may be included in this investigation if they meet the following criteria:

- Principal Investigator is credentialed in catheter ablation and femoral arterial cannulation in a hospital with an interventional vascular specialist who is credentialed in renal artery interventions. The vascular specialist is to be immediately on-call during the renal denervation procedure to assist as needed in renal artery cannulation, catheter manipulation within the renal artery, and managing any vascular adverse events such as renal artery perforation or dissection.

- Principal investigator has experience using the Arctic Front®/ Arctic Front Advance/Arctic Front Advance Pro Cardiac Cryoablation Catheter system in at least 10 cases.
- Center has a Medtronic CryoCath CryoConsole installed at the facility (Generation 5 console).
- Willingness to perform both pulmonary vein isolation ablation with the Arctic Front Advance/Arctic Front Advance Pro Cardiac Cryoablation Catheter system and renal artery denervation with the Symplicity Spyral Catheter and Symplicity G3 Generator during the same case.
- Principal investigator has access to an adequate number of potential subjects.
- Sufficient experienced staff and equipment (e.g. study coordinator, renal duplex ultrasound, renal angiography, and trans-thoracic echocardiogram (TTE)) to execute and maintain protocol compliance.

6.2 Center activation

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

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

- Medtronic and IRB/MEC approval (and membership roster/voting list, as required by local law) of the current version of the CIP and Informed Consent Form, subject facing materials, Report of Prior Investigation as required by local laws and other materials, as necessary
- Regulatory authority approval or notification (as required per local law)
- Fully executed Clinical Trial Agreement (CTA)
- Investigator Curriculum Vitae (CV)
- Delegation of center personnel responsibilities
- Documentation of study training
- Financial Disclosure

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

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

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

6.3 Equipment requirements

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

- Trans-thoracic echocardiogram

- Renal angiography
- Renal duplex ultrasound

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

The sponsor will supply all required study materials for appropriate data collection before study start, like the office blood pressure monitors (OBPs). Medtronic will control the supply of devices and study materials

6.4 Role of the sponsor representative during study procedures and follow up visits

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

- Provide study training relevant and pertinent to the involvement of personnel conducting study activities and investigator responsibilities
- Technical support at the pulmonary vein isolation, renal denervation and Reveal LINQ insertion procedures under the supervision of a study investigator, but no data entry, shall be performed by Medtronic personnel or their representatives at sites
- Monitoring and auditing activities
- Follow up visit activities involving the Reveal LINQ device and CareLink

6.5 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 5.

Table 5: Data collection and study procedure requirements at subject visits

												Repeat cryoablation Procedure (0-90 days), if performed		
	Enrollment/Baseline	**CT Scan**	**Cryoablation Procedure**	**Renal Artery Denervation**	**Reveal LINQ Insertion**	**Hospital Discharge**	**1 month**	**6 month**	**Every 6 months until study end closure12 month**	**Unscheduled**	**Exit**	**Baseline**	**Cryoablation**	**Hospital Discharge**
Informed Consent	x													
Inc/Exc criteria	x	x		x								x		
Medical history	x													

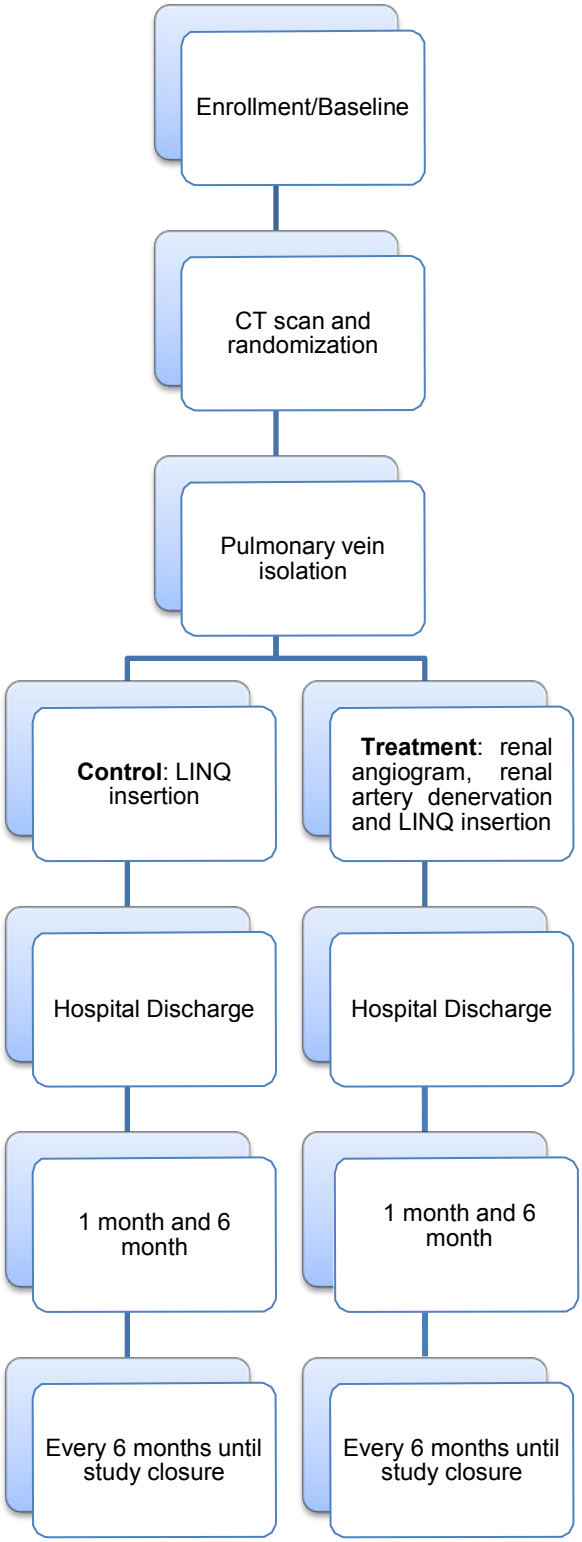
												Repeat cryoablation Procedure (0-90 days), if performed		
	Enrollment/Baseline	**CT Scan**	**Cryoablation Procedure**	**Renal Artery Denervation**	**Reveal LINQ Insertion**	**Hospital Discharge**	**1 month**	**6 month**	**Every 6 months until study end closure12 month**	**Unscheduled**	**Exit**	**Baseline**	**Cryoablation**	**Hospital Discharge**
Physical exam	x						x	x	x	x		x		
Trans-Thoracic Echocardiogram	x (1)													
Review medications	x					x	x	x	x	x	x	x		x
Office BP x3	x						x (8)	x (8)	x (8)	x		x		
Blood and urine labs: Serum Creatinine (sCr), Spot urine albumin and creatinine and Cystatin C	x					x	x	x		x (2)				
Review of symptoms	x						x	x	x	x				
Randomization		x												
Pregnancy test	x (3)													
Transesophageal Echocardiogram (TEE) (3)			x (4)											
Renal angiogram for Treatment group only				x										
Procedure information		x	x	x	x								x	
CareLink in-office interrogation (5)						x (6)	x	x	x	x				
CareLink manual home transmission							x (5)				x			
Renal Artery Imaging-Duplex Ultrasound								x (7)						
Adverse Events, Reveal LINQ System Modification, Death, Study Deviation, Device Deficiencies	As they occur													

1. For subjects with persistent AF, perform during the 12 month interval preceding the Consent Date, or between Consent Date and Procedure Date.
2. Optional, if performed.
3. Perform within 5 days prior to the Procedure.
4. TEE at baseline to assess for LA thrombus as indicated by the 2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation (Section 6.7).
5. CareLink transmissions need to occur at a minimum one time per month. For the monthly CareLink transmissions that coincide with a scheduled follow-up visit (i.e. 1 or 6-month visits), a monthly transmission

is not required but perform an in-office device interrogation and data transfer to Medtronic. A CareLink transmission may be used as a substitute for an in-office device interrogation.

6. Ensure a device interrogation with final programmed settings is transferred to Medtronic. This may be at the time of insertion or prior to hospital discharge.
7. Only for subjects who underwent the renal denervation procedure (randomized to the Treatment group). If clinically significant renal artery stenosis is suspected, a follow-up renal angiogram will be performed.
8. Office blood pressure (according to guidelines in Appendix G), needs to be obtained if an office visit occurs or during alternative methods of data collection as described in section 6.18.1.

Figure 1: Study design flowchart



6.6 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 Consent and an Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language as required by law that has been approved by the investigational center's IRB/MEC and signed and dated by the subject (or their legally authorized representative, US ONLY). 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 IRB/MEC will be required to approve the Consent Form, 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 IRB/MEC. Any adaptation of the sample Consent Form must be reviewed by Medtronic and the IRB/MEC reviewing the application prior to enrolling subjects. Refer to Appendix D: Informed consent templates for the sample Consent Form.

Prior to initiation of any study-specific procedures, patient informed consent must be obtained from the subject (or their legally authorized representative or guardian). The informed consent process must be conducted by the principal investigator or an authorized designee, and 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

In Europe, 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. It is also best practice to document in the subject's case history if they were re-consented for any reason.

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. In Europe, when a subject cannot read and/or write, an independent witness shall be present throughout the process, the written PIC Form and any other information shall be read aloud and explained to the prospective subject. The subject should "make his mark" (sign or otherwise physically mark the document so as to indicate consent) on the Consent Form 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.

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 Medtronic Field personnel who support study procedures must be able to review the subject's signed and dated Consent Form and verify its completeness prior to proceeding with study procedures. In the event the Medtronic Field personnel identify patient informed consent as being incomplete, the study procedures will not be allowed to occur until the consent of the subject can be adequately and appropriately obtained.

Any changes to a previously approved Informed Consent Form throughout the course of the study must be approved by Medtronic and the IRB/MEC reviewing the application before being used to consent a prospective study subject. The document(s) must be controlled (i.e. versioned and/or dated) to ensure it is clear which version(s) were approved by the IRB/MEC. All important new information should be provided to new and existing subjects throughout the study.

6.7 Medications

The collection of the following medications will take place during the course of this study: anticoagulants, those prescribed to treat atrial fibrillation, including those used for rate control, and those prescribed to treat hypertension. Information collected will include the medication name, purpose and start/stop dates.

It is recommended to maintain all randomized subjects on their baseline hypertensive medications without changes until the 6-month visit. A study deviation is not required if changes are made to these medications.

If a subject is on amiodarone, it is recommended to take them off 4-6 weeks before the end of the 90-day post cryoablation procedure blanking period.

It is recommended that subjects be off all antiarrhythmic medications within 90 days post cryoablation procedure.

Medication changes that occur specifically because the subject will undergo the study procedures should not be recorded.

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

6.8 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 Authorization to Use and Disclose Personal Health Information/Research Authorization must be documented. The following evaluations will be performed after consent, unless previously performed as part of routine clinical evaluations within the specified windows:

Within 12 months prior to the consent date or between consent date and procedure date

If the subject has a diagnosis of persistent AF, confirm the left atrial volume index is ≤ 40 ml/m^2 by a trans-thoracic echocardiogram.
A trans-thoracic echocardiogram on file can be used providing it is within the last year from the date of consent, if not, perform a trans-thoracic echocardiogram.

After consent date but before the procedure date

- Assessment of all factors specified for evaluation under Inclusion Criteria and Exclusion Criteria (Section 5.2).
- Medical history including: assessment of risk factors, NYHA cardiac functional class, systemic history and cardiovascular history, assessment of atrial fibrillation history and symptoms and other arrhythmic episodes
- Physical examination: height, weight, and heart rate.
- Office blood pressure: To assess if the average of 3 office systolic blood pressures measured per guidelines (Appendix G: Blood Pressure Measurement Procedures) is > 140 mmHg.
    - If a subject's average of 3 systolic blood pressures is ≤ 140 mmHg, then repeat blood pressure measures (according to Appendix G: Blood Pressure Measurement Procedures) are allowed up to two times over the subsequent 2 weeks. Any subjects with an average office systolic blood pressure ≤ 140 mmHg after a total of three attempts will be excluded from the study.
    - For instructions on blood pressure measurement, see Appendix G: Blood Pressure Measurement Procedures.
    - This will be the baseline measurement for statistical comparison and inclusion criteria
- Laboratory testing: Subjects should be instructed to avoid eating or drinking caffeine or alcohol for 10-12 hours prior to lab testing but should drink water normally (avoid other liquids) and take prescribed medications during this time.
    - Serum creatinine (sCr) to calculate eGFR for eligibility criteria and as a factor of baseline kidney function. eGFR should be calculated using the Modification of Diet in Renal Disease (MDRD) Formula: eGFR (mL/min/1.73 m^2)=175 x (sCr/88.4)-
      1.154 x (Age)-0.203 x (0.742 if female) x (1.212 if of African descent) (SI units).
    - Subjects with eGFR <30 mL/min/1.73m^2 will be excluded from the study.

- Spot urine albumin and creatinine to evaluate the albumin to creatinine ratio (UACR) as a factor for baseline kidney function.
- Blood test: Cystatin C to help detect and monitor acute and chronic kidney dysfunction.

- Confirm the subject has eligible renal anatomy via computerized tomography (CT scan)
  - Perform randomization after eligibility has been confirmed, see Section 6.9.

Performed within 5 days prior to the procedure date

- Blood or urine test-Serum or urine human chorionic gonadotropin (hCG) Pregnancy test to confirm negative pregnancy status of females of childbearing potential.
- Transesophageal Echocardiogram (TEE)

  Prior to undergoing an AF ablation procedure, a TEE should be performed in all subjects with atrial fibrillation more than 48 hours in duration or of an unknown duration if adequate systemic anticoagulation has not been maintained for at least 3 weeks prior to the ablation procedure.

  Performance of a TEE in subjects who are in sinus rhythm at the time of ablation or subjects with AF who are in AF but have been in AF for 48 hours or less prior to AF ablation may be considered but is not mandatory.

  Subjects noted to have left atrial thrombus on TEE will not undergo the procedure and will be exited from the study unless thrombus resolution is confirmed on a repeat TEE.

6.9 Randomization

Randomization schedules will be prepared for each site using a random permuted block design stratified by center and AF diagnosis. The schedules will allocate subjects in a 1:1 ratio to the treatment or control arm.

Each center will receive a set of sequentially numbered envelopes labeled specifically for that center that is labeled with one randomization code per envelope. After a CT scan has been performed and confirmed that the renal anatomy meets eligibility requirements, the subject will be randomized.

The next sequential envelope labeled with a randomization code will be used. The envelope number will be recorded for each randomized subject and communicated to Medtronic. The sequence of subject randomization will be checked to ensure it matches the sequence of envelope numbers.

Randomization assignments are the following:

- Treatment:
  - Perform the pulmonary vein isolation procedure, renal angiogram, renal artery denervation procedure and the Reveal LINQ insertion.
- Control:

- Perform the pulmonary vein isolation procedure and the Reveal LINQ insertion. Do NOT perform renal denervation.

Enrolled subjects who were not randomized should be exited. See Section 9.2.2 if the subject has an ongoing adverse event.

Subjects and center personnel will be blinded to the randomization assignment until after the pulmonary vein isolation procedure.

Crossing over to the Treatment group once assigned to the Control group is not allowed at any point during the study.

6.10 Pulmonary vein isolation procedure

Perform the pulmonary vein isolation procedure first using Arctic Front Advance/Arctic Front Advance Pro. Investigator is to perform the procedure according to the procedural steps in this protocol and the Instructions for Use for the Arctic Front Advance/Arctic Front Advance Pro Cardiac Cryoablation System. Appropriate systemic anticoagulation and sedation should be attained at the investigators discretion according to their institutions pre- established procedures/guidelines at the time of the procedure. Current recommendations for anticoagulation are found in the 2012 Expert Consensus Statement on the Ablation of atrial fibrillation.[17]

6.10.1 Diaphragm Movement

a. Phrenic nerve pacing or other phrenic nerve monitoring technique must be done for each cryoapplication, specifically those cryoapplications surrounding the RS and RI pulmonary veins

b. Prior to the first cryoablation application, the Investigator will make a fluoroscopic recording of inspiratory and expiratory movement of the diaphragm

c. After the last cryoablation application, the investigator will make a fluoroscopic recording of the inspiratory and expiratory movement of the diaphragm

6.10.2 Balloon Pulmonary Vein (PV) Cryoablation

a. Every effort consistent with subject welfare will be made to treat all PVs or their anomalous equivalents.
b. The Arctic Front Advance/Arctic Front Advance Pro Cardiac Cryoablation Catheter will then be advanced into the LA and inflated. Once inflated, the catheter will be tracked over the wire and positioned at the entrance of the PV.
c. Assess the positioning, contact and occlusion of the PV by the catheter's balloon by ultrasound imaging, injection of contrast material or other technique. Reposition as needed.
d. After one or more cryoapplications, each pulmonary vein should be minimally assessed for entrance block and, where assessable, exit block to demonstrate the cryoablation procedure endpoint of electrical isolation of the four major PVs.

6.10.3 Gap or Touch Up Ablation

At the Investigator's discretion, a focal cryocatheter or a radio frequency catheter may be performed to complete electrical isolation of one or more PVs.

6.10.4 Other Ablations

Subjects may have other cardiac rhythm abnormalities requiring treatment detected during the ablation procedure. This may include right/left atrial flutter or atrial fibrillation triggers. Treatment of such abnormalities is at the Investigator's discretion. Such ablation will be fully documented in the relevant CRF.

6.10.5 Procedure Documentation

During the procedure the investigator will document the following:

a. Catheter used for each ablation (i.e. Arctic Front Advance/Arctic Front Advance Pro, Freezor *MAX* or radiofrequency)

b. Temperature for each application

c. Duration of each application

d. Vein location for each application (e.g. right superior pulmonary vein)

e. Use of phrenic nerve pacing or other phrenic nerve monitoring technique for each application, specifically those applications surrounding the RS and RI pulmonary veins

f. Demonstrated electrical block

g. Adjunctive mapping or visualization devices, sedation type, procedure information, fluoroscopy time, contrast dye amount and concentration will be collected.

6.11 Peri – procedural anticoagulation

Heparin should be administered prior to or immediately following transseptal puncture during AF ablation procedures and adjusted to achieve and maintain an ACT of 300 to 400 seconds.

Performance of AF ablation in subjects systemically anticoagulated with warfarin does not alter the need for intravenous heparin to maintain a therapeutic ACT during the procedure.

Administration of protamine following ablation to reverse heparin may be considered.

6.12 Renal angiography

Perform renal angiography if randomized to Treatment, following the pulmonary vein isolation procedure.

Subjects should be prepped for a renal angiography according to standard procedures. For subjects with chronic kidney disease and/or risk factors for contrast-induced nephropathy (CIN), the hospital's standard-of-care protocol for CIN prevention should be utilized.

An aortogram and selective renal angiography will be performed to confirm renal artery anatomy. Anatomic eligibility is defined as each kidney having at least one renal artery ≥3mm and ≤8mm in diameter and minimum treatable length per the Symplicity Spyral Catheter Instructions for Use, without significant stenosis or other abnormality. *NOTE: All renal arteries with ≥3 mm and ≤ 8 mm diameter with minimum treatable length per the Symplicity Spyral Catheter Instructions for Use shall be*

treated, including dual renal arteries meeting these morphologic criteria.

6.13 Renal artery denervation procedure

If randomized to Treatment, the renal artery denervation procedure will be performed according to the supplied Symplicity Spyral Catheter Instructions for Use, Symplicity G3 Generator User Manual and associated training provided by Medtronic.

Prior to this procedure, appropriate systemic anticoagulation and sedation should be attained. Blood pressure and heart rate should be closely monitored throughout the procedure. Investigators may choose to apply treatment to any renal artery that meets the anatomy eligibility criteria. The Symplicity Spyral Catheter will be delivered to the renal artery and the ablation treatments at multiple positions along the renal artery will be performed according to the procedures described in the Instructions for Use.

Provide one copy of the renal angiogram cine procedure to Medtronic.

Sedation type, procedure information, fluoroscopy time, contrast dye amount and concentration will be collected.

6.14 LINQ insertion

Before the subject is discharged from the hospital, preferable while still in the EP lab, insert the Reveal LINQ device. The insertion procedure will be performed in accordance with the hospital's standard practice and in accordance with the Medtronic Reveal LINQ manual. Program Device Data Collection parameters and verify device sensing performance is acceptable. Subjects with an existing Reveal LINQ device may be enrolled if they have a minimum of 1 year remaining battery life. Ensure the device is programmed to the settings below.

6.14.1 Programming Requirements

Required programming:

Parameter	Required Setting
Reason for Monitoring	AF ablation
Type of AT/AF detection	AF only
AF Detection	Balanced sensitivity
AT/AF Record of ECG of	All episodes
Ectopy Rejection	Nominal

Recommended programming:

Parameter	Required Setting
Tachy detection	OFF
Brady detection	OFF
Pause detection	OFF

Perform a device interrogation and data transfer (e.g. save-to-disk, USB data transfer) with the final programmed settings. Final interrogation may be performed at hospital discharge. Ensure, at a minimum, Medtronic receives an interrogation with the final programmed settings.

6.15 Device deficiencies

A device deficiency is defined as inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. NOTE: Device deficiencies include malfunctions, use errors and inadequacy in the information supplied by the manufacturer including labeling. Device deficiencies that do not adversely affect the subject should be reported to Medtronic as a device deficiency and not as an adverse event. If the device deficiency is a reportable adverse event, the event should be reported as an adverse event not a device deficiency. Report device deficiencies for all Medtronic products used.

6.16 Hospital discharge

Prior to discharge, the following shall be collected: blood and urine samples, assess medications, assess adverse events, and review study requirements with the subject to help ensure compliance with follow-up procedures.

The use of CareLink will then be reviewed and training will be given prior to discharge to the subject.

Systemic anticoagulation with warfarin or a direct thrombin or Factor Xa inhibitor is recommended for at least two months following the AF ablation procedure.
Decisions regarding the continuation of systemic anticoagulation agents more than two months following ablation should be based on the subject's risk factors for stroke and not on the presence of AF. Discontinuation of systemic anticoagulation therapy post ablation is not recommended in subjects who are at high risk of stroke as estimated by currently recommended schemes (CHADS2 or CHA2DS2VASc).

6.17 Scheduled follow-up visit windows

After receiving notice of a subject pulmonary vein isolation procedure, Medtronic will provide the target dates and windows to complete each visit either to the center, in-home, virtually or by phone. 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 data collected at late and early follow-up visits. Therefore, a late or early visit is preferred over a missed visit but must be accompanied by a deviation. Subjects will be followed until all subjects who underwent a pulmonary vein isolation procedure reach the 6-month visit.

Table 6: Follow up visit windows

Study Follow-up Visit	**Window (Calculated days post-procedure attempt)**		
	Window Start (# of days)	Target (# of days)	Window End (# of days)
1 month	30	30	46
6 month	180	180	194
12 month	335	365	395
18 month	515	545	575
24 month	700	730	760
30 month	880	910	940

36 month	1065	1095	1125
42 month	1245	1275	1305

Additional windows will be sent to centers if they extend beyond 42 months.

6.18 Scheduled in-office follow-up visits

6.18.1 One, Six and Every Six Month Visit Until Study Closure

It is recommended that anti-hypertensive medications and dose not be changed through the 6 month visit unless medically necessary. It is recommended that subjects be off all antiarrhythmic medications within 90 days post cryoablation procedure.

The following will be collected:

- blood and urine samples (not required after the 6 month visit)
- physical exam
- vital signs (including 3 blood pressure measurements according to Appendix G: Blood Pressure Measurement Procedures)
- review of medications
- assess for adverse events
- assess arrhythmias and symptoms, episodes of medical care suggestive of arrhythmia including hospitalizations, office or ER visits, or any AF-related procedures such as cardioversions or additional ablations
- interrogate the Reveal LINQ device, review prior CareLink reports and the current interrogation for possible AF related events

Alternative methods of data collection may be necessary in the case of extenuating circumstances, such as a global pandemic, when subjects are prohibited from coming into the office for required assessments. For all assessments completed via alternative methods in these circumstances, sites are not required to enter a protocol deviation for missing, alternative, and/or late data collection. Data unable to be collected remotely or via an alternative method should be collected at the next possible in-person visit.

In the event a subject is unable to return for an in-office follow-up visit, the alternative methods of obtaining follow-up assessments are listed below:

- In-home visit by trained and delegated site personnel or designee, i.e. home health care personnel. The following assessments may not be completed with an in-home visit:
  - CareLink in-office interrogation. Guide a subject through a full interrogation (“Interrogate All”) at the end of the follow-up visit
  - Renal Artery Imaging:
    - Make every effort to schedule in-person renal artery imaging as soon as possible.

When possible, subjects may be referred to a local imaging center for assessment. Local imaging technicians would require study training and delegation prior to assessment. In the event an in-home visit is not possible, the alternate methods for obtaining follow-up assessments are listed below:

- Virtual Visit, i.e. inclusive of video with study subject.
  - The following assessments may not be completed with a virtual visit:
    - Physical examination, limited review to be completed per physician discretion.
    - CareLink in-office interrogation. Guide a subject through a full interrogation (“Interrogate All”) at the end of the follow-up visit.
    - Laboratory Tests:
      - When possible, the subject should be referred to a local laboratory to collect samples. Laboratory Kits to be provided to subjects in advance of the visit by study site.
    - Renal Artery Imaging:
      - Make every effort to schedule in-person renal artery imaging as soon as possible.
      - When possible, the subjects could be referred to a local imaging center for assessment. Local imaging technicians would require study training and delegation prior to assessment.

  - Office blood pressure unit to be provided to the subjects in advance of the visit by study site. Measurements collected by the patient may be collected and designated in the case report form.

- Phone visit, i.e. no video with the subject.
  - The following assessments may not be completed with a phone visit:
    - Physical examination limited review to be completed per physician discretion.
    - CareLink in-office interrogation. Guide a subject through a full interrogation (“Interrogate All”) at the end of the follow-up visit
    - Laboratory Tests:
      - When possible, the subject should be referred to a local laboratory to collect samples. Kits to be provided to subjects in advance of the visit by study site.
    - Renal Artery Imaging
      - Make every effort to schedule in-person renal artery imaging as soon as possible.
      - When possible, the subjects could be referred to a local imaging center for assessment. Local imaging technicians would require study training and delegation prior to assessment.

  - Office blood pressure unit to be provided to the subjects in advance of the visit. Measurements may be collected and designated as patient reported in the case report form.

6.18.1.1 Six month renal artery duplex ultrasound (Treatment group only)

Renal artery duplex ultrasound (DUS) imaging will be performed only for subjects who underwent the renal artery denervation. DUS will be conducted as per the DUS protocol provided by the DUS Core Lab. The DUS will be assessed and if clinically significant stenosis (e.g. renal artery to aorta peak systolic velocity ratio >3.5, or peak systolic velocity >200 cm/s with evidence of post-stenotic turbulence)

is indicted, angiography will be performed. A Core Lab will be responsible for comparing 6 months angiogram with baseline angiography to evaluate any potential renal artery stenosis.

6.18.2 Atrial Arrhythmia Management

Subjects are required to have their Reveal LINQ interrogated monthly via CareLink transmissions. For the monthly CareLink transmissions that coincide with a scheduled follow-up visit (i.e. 1 or 6-month visits), a CareLink transmission is not required but a device interrogation and data transfer either by save-to-disk or USB data transfer should be performed at the follow-up visit. A CareLink transmission may be used as a substitute for an in-office device interrogation. If CareLink transmissions become unavailable, centers may be required to submit CareLink reports to Medtronic by uploading them to a secure server or by sending printed versions of the reports. Complete a final manual transmission upon study exit.

6.19 Unscheduled follow-up visits

An unscheduled visit is defined as any study-related visit which does not occur within the designated visit window of a scheduled follow up visit. Subjects who are seen outside of their regularly scheduled follow up visit for arrhythmia symptoms or suspected symptoms associated with renal denervation should have unscheduled procedures and data collection completed.

The following will be collected:

- blood and urine samples (optional)
- physical exam
- vital signs (including 3 blood pressure measurements according to Appendix G: Blood Pressure Measurement Procedures)
- review of medications
- assess for adverse events
- assess arrhythmias and symptoms, episodes of medical care suggestive of arrhythmia including hospitalizations, office or ER visits, or any AF-related procedures such as cardioversions or additional ablations
- interrogate the Reveal LINQ device, review prior CareLink reports and the current interrogation for possible AF related events

6.20 System modification for Reveal LINQ

A system modification will be reported in the event the Reveal LINQ requires invasive modification (e.g. reposition, explant, replacement). In the event of a system modification, the follow-up visit schedule for the subject will remain unchanged. If the device is explanted and a replacement will not be inserted, the subject should continue to stay in the study.

6.21 Permissible repeat ablation

All subjects may have one repeat ablation procedure within Days 0-90 after the first ablation if the following criteria are met:

- Inclusion criteria:
    - Recurrent or a new onset atrial tachycardia

- Exclusion Criteria:
  - Active systemic infection
  - Condition where manipulation of the catheter within the heart would be unsafe (e.g. intracardiac mural thrombus)
  - Cryoglobulinemia
  - Myocardial infarction, unstable angina pectoris, syncope, PCI/PTCA, or coronary artery stenting within 3 months of the repeat ablation
  - Cerebrovascular accident or TIA within 1 month of the repeat ablation
  - Presence or a permanent pacemaker, biventricular pacemaker, atrial defibrillator or any type of implantable cardiac defibrillator (with or without biventricular pacing function)

- Re-ablation assessment is performed as follows:
  - Physical examination, NYHA cardiac functional class, office blood pressure and review of medications and symptoms.
  - Study status post re-ablation: The subject's procedures and follow up visit/assessments will continue based on the initial cryoablation procedure date. A re-ablation of a study subject under this section is not an AF Intervention.

Other ablation techniques may be used as outlined in Section 6.10.

6.22 Repeat renal artery denervations

Repeat renal artery denervations are not allowed at any point during the study.

6.23 Recurrence of atrial fibrillation

Documentation of AF recurrence must be provided to the sponsor and additional source documents may be requested. Documentation of AF must include the following:

- Reveal LINQ rhythm recording (EGM)

6.24 Study exit

Contact the subject to review medications, adverse events, episodes of medical care suggestive of arrhythmia including hospitalizations, office or ER visits, and any AF-related procedures such as cardioversions or additional ablations. Have the subject manually transmit data from their Reveal LINQ device at study exit.

Subjects may be exited from the study for any of the following situations:

- Subject has completed follow-up
- Subject with LINQ battery at end of life, having completed at least 6 months of study follow-up
- Subject lost to follow-up
- Subject death
- Subject did not meet inclusion/exclusion criteria

- Subject not randomized
- 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)

Once a subject is randomized, all efforts should be made to continue following the subject until study closure.

6.24.1 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.

6.24.2 Subject-Initiated Withdrawal

If subject chooses to withdraw, document date and reason for exit.

6.24.3 Early Exit for Any Reason

Prior to an early exit of a subject from the study, all efforts should be made to continue following the subject until all serious unresolved procedure or device related adverse events, as classified by the investigator, are resolved or they are unresolved with no further actions planned. Report any changes to the outcome before exiting the subject.

7. INVESTIGATIONAL DEVICE STORAGE, HANDLING AND TRACEABILITY

7.1 Symplicity Spyral Renal Denervation System

In Europe, the study will utilize the commercially available Symplicity Spyral Renal Denervation System (Symplicity Spyral Catheter and Symplicity G3 Generator) with no study driven changes to the product or labeling and are considered non-investigational. Product ordering is the responsibility of the center personnel. The products may be stored the same as other commercially released product.

In the US, components of the Symplicity Spyral Renal Denervation System are considered investigational. Investigational product will be distributed to a center only when Medtronic has received all required documentation and has notified the center of center readiness. Distribution of the investigational product to study centers during the clinical study will be managed by Medtronic. Investigational product must be stored in a secure location at the center. It is the responsibility of the investigator to correctly handle, store, and track the investigational products. Investigational products will be used only in the study according to the CIP.

For the US, sites, all Symplicity Spyral Renal Denervation System components used/attempted will be tracked and must be treated as investigational for this

study. Investigational product disposition logs will be provided to the center and used for tracking of all investigational products during the study. The investigational product distribution logs are to be used for the Symplicity Spyral Catheter, Symplicity G3 Generator, power cord and foot switch. The logs must be maintained at each US center and updated when investigational product is received, opened, used/attempted, disposed of or returned to Medtronic, see Table 7.

7.2 Arctic Front Advance and Freezor *MAX* Cardiac Cryoablation Catheters

In Europe, the study will utilize the market-released Arctic Front Advance/Arctic Front Advance Pro and Freezor *MAX* Cardiac Cryoablation Catheters with no study driven changes to the product or labeling and are considered non-investigational. Product ordering is the responsibility of the center personnel. The products may be stored the same as other commercially released product.

In the US, the Arctic Front Advance/Arctic Front Advance Pro and Freezor *MAX* Cardiac Cryoablation Catheters will be considered investigational when used in the persistent AF population with an AF episode duration of 6 months or longer, however, tracking of the catheter will start when the packaging is opened with the intention of using for the clinical study, regardless of the subjects AF diagnosis. Product ordering will be the responsibility of center personnel. The products may be stored the same as other commercially released product. It is the responsibility of the investigator to correctly track the products.

In the US, product disposition logs will be provided to the center and used for tracking of the Arctic Front Advance/Arctic Front Advance Pro and Freezor *MAX* Cardiac Cryoablation Catheters. The logs must be maintained at each center and updated when product is opened, used/attempted, disposed of or returned to Medtronic, see Table 7.

7.3 Final product disposition

In the US, all unused Symplicity Spyral Renal Denervation System components must be returned to Medtronic upon study closure at the center or earlier. The product disposition log must be updated with the final device disposition. If any Medtronic products are suspected in a device deficiency or Unanticipated Adverse Device Effect (UADE), make every effort to return them to Medtronic. Contact your local Medtronic field personnel or clinical study manager to receive a return mailer kit if used product needs to be sent back to Medtronic.

Table 7: US Product tracking requirements

	Symplicity Renal Denervation System (Symplicity Spyral Catheter, Symplicity G3 Generator, power cord and foot switch)	Cardiac Cryoablation Arctic Front Advance/Arctic Front Advance Pro and Freezor *MAX* Catheters
Receipt	x	
Opened	x	x

Used/Attempted	x	x
Unopened	x	
Returned or disposed	x	x

8. STUDY DEVIATIONS

A study deviation is defined as an event within a study that did not occur according to the CIP or CTA.

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). A study deviation is not required if a subject misses a monthly LINQ manual interrogation.

All study deviations must be reported on the CRF 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 IRB/MEC as well as Medtronic within five working days. Reporting of all other study deviations should comply with IRB/MEC policies and must be reported to Medtronic as soon as possible upon the center becoming aware of the deviation. Refer to Investigator Reports, Table 11 for specific deviation reporting requirements and timeframes for reporting to Medtronic and the applicable regulatory body(s).

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

9. ADVERSE EVENTS AND DEVICE DEFICIENCIES

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

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

collection and reporting of safety information.

9.1 Adverse event and device deficiency definitions

Where the definition indicates “device”, it refers to any device used in the study. This might be the devices under investigation or any market released component of the two systems.

For the purpose of this study, all Adverse Events (AEs) and Device Deficiencies (DDs) will be classified according to ISO 14155:2011.

Table 8: Adverse event definitions

General	
Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects whether or not related to the investigational medical device. (ISO 14155:2011 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 a medical device (ISO 14155:2011 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 medical device. *Note 2*: This definition includes any event resulting from an error use or from intentional misuse of the medical device.
Hospitalization	A hospital admission lasting more than 24 hours or which includes an overnight admission.

Relatedness	
Procedure related	An adverse event that occurs due to any portion of the cryoablation or renal denervation procedures related to the study. **Cryoablation procedure related**: event is related to any portion of the procedure that encompasses cryoablation. **Renal angiogram**: event is related to any portion of the procedure that encompasses the renal angiogram. **Renal denervation procedure related**: event is related to any portion of the procedure that encompasses renal denervation. **Reveal LINQ insertion procedure related**: event is related to any portion of the procedure that encompasses insertion of the Reveal LINQ device. **Procedure related**: if it cannot be determined which portion of the procedure an event is related to.

System related	**Cryoablation system related**: event that results from the presence or performance (intended or otherwise) of the cryoablation system. **Symplicity Renal Denervation system related**: event that results from the presence or performance (intended or otherwise) of the Symplicity Renal Denervation system (Symplicity Spyral Catheter and Symplicity G3 Generator). **Reveal LINQ system related**: event that results from the presence or performance (intended or otherwise) of the Reveal LINQ device. **Other system related**: An adverse event that results from the presence or performance (intended or otherwise) of any device/tool used not related to the cryoablation, renal angiogram, renal denervation procedure or Reveal LINQ system.
Cardiovascular related	An adverse event relating to the heart and the blood vessels or circulation.
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, an (investigational) device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the CIP or applicable (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. (21 CFR 812.3(s))
Serious Adverse Event (SAE)	Adverse event that a) led to death, b) led to serious deterioration in the health of the subject, that either resulted in • 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 a body structure or a body function, b) led to fetal distress, fetal death or a congenital abnormality or birth defect (ISO 14155:2011 3.37) *NOTE*: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.
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)

Complication	An adverse event that results in death, involves any termination of a significant device function, or requires intervention. **Noninvasive**: noninvasive, when applied to a diagnostic device or procedure, means one that does not by design or intention: (1) Penetrate or pierce the skin or mucous membranes of the body, the ocular cavity, or the urethra • Penetrate: to pass, extend, pierce, or diffuse into or through something; to enter by overcoming resistance; to gain entrance to • Pierce: to force a way into or through something or (2) enter the ear beyond the external auditory canal, the nose beyond the nares, the mouth beyond the pharynx, the anal canal beyond the rectum, or vagina beyond the cervical os. For purpose of this part, blood sampling that involves simple venipuncture is considered noninvasive, and the use of surplus samples of body fluids or tissues that are left over from samples taken for non-investigational purposes is also considered noninvasive. (21 CFR 812.3(k))
Observation	Any adverse event that is not a complication.
Timing	
Pre-procedure	An adverse event that occurs after the consent form has been signed but before access to the vasculature has occurred for the study required procedures.
Cryoablation-procedure	An adverse event that occurs during the cryoablation procedure from the time of the first sheath access to the vasculature until the last sheath for cardiac ablation is removed.
Renal angiogram-procedure	An adverse event that occurs during the renal angiogram procedure from the time of the first sheath access to the vasculature for the angiogram until the last sheath for angiogram is removed.
Renal denervation-procedure	An adverse event that occurs during the renal denervation procedure from the time of the first sheath access to the vasculature until the last sheath for renal denervation has been removed.
Post-cryoablation/Post-renal denervation	An adverse event that occurs after the removal of all cardiac ablation, renal denervation and EP catheters used in the procedures.
Other	
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 and inadequate labeling.
Unavoidable Adverse Event	An Adverse Event inherent to a surgical procedure that is expected to occur in all subjects for a projected duration according to the Investigator's opinion, including, but not limited to those provided below. These are not reportable AEs unless they occur after or last longer than the timeframe. If any other events below are classified as serious they must be reported as an adverse event.

Event Description	Timeframe (hours) from the Surgical Procedure
Anesthesia related nausea / vomiting	24
Low-grade fever (<100°F or 37.8°C)	48
Incisional pain	72
Mild to moderate bruising / ecchymosis	168
Sleep problems (insomnia)	72
Back pain related to laying on table	72
Shoulder/arm/leg pain/discomfort/stiffness related to immobilization during procedure	72

9.2 Adverse event and device deficiency assessment

9.2.1 Adverse Events

To ensure that all AEs which are potentially relevant are collected, all system related, procedure related, cardiovascular related and serious AEs will be collected throughout the study duration, starting at the time of signing the consent form. Reporting of these events to Medtronic will occur on an AE form, including a description of the AE, date of AE onset, treatment, resolution, and assessment of both the seriousness and the relatedness to the device.
Exceptions include:

- Documented pre-existing conditions are not considered AEs unless the nature or severity of the condition has worsened
- Recurrence of AF event unless an invasive action was taken
- Unavoidable AEs unless the AE worsens or is present outside the stated timeframe listed in Table 8

For AEs that require immediate reporting (see Table 9: Adverse Event Reporting), initial reporting may be done by phone, fax, email or on the CRF completing as much information as possible. The completed AE CRF must be submitted to Medtronic as soon as possible. Each AE must be recorded on a separate AE Form. Subject deaths are also required to be reported. Refer to Section 9.5 for Subject Death collection and reporting requirements.

9.2.2 Device Deficiency

Device deficiency information will be collected throughout the study and reported to Medtronic. Note that device deficiencies that result in an adverse device effect (ADE) to the subject should be captured as an Adverse Event only.

Device deficiencies that did not lead to an AE but could have led to a Serious Adverse Device Effect (SADE) (i.e., if suitable action had not been taken, if intervention had not been made, or if the circumstances had been less fortunate) require immediate reporting (see Table 9).

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.

9.2.3 Processing Updates and Resolution

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

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

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

9.3 Market-released reporting requirements

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

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

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

Medtronic will notify the regulatory authorities as applicable for the following incidents immediately upon learning of them:

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

9.4 Adverse event and reporting requirements

Regulatory reporting of AEs will be completed according to regulatory requirements. Refer to Table 9: Adverse Event Reporting for a list of required investigator reporting requirements and timeframes, and of required Medtronic reporting requirements and timeframes.

It is the responsibility of the investigator to abide by any additional AE reporting requirements stipulated by the IRB/MEC.

For AEs that require immediate reporting, initial reporting may be done by contacting the study sponsor per the sponsor contact information provided in this document.

Table 9: Adverse Event and Device Deficiency Reporting Requirements

Unanticipated Adverse Device Effects (UADEs)	
Investigator submit to:	
Medtronic	US: Submit as soon as possible, but no later than within 10 working days after the investigator first learns of the event. (21 CFR 812.150(a)(1)) Europe: Immediately after the Investigator first learns of the event or of new information in relation with an already reported event.
IRB/MEC	US: Submit as soon as possible, but no later than within 10 working days after the investigator first learns of the event. (21 CFR 812.150(a)(1)) Europe: Submit to MEC per local reporting requirement.
Regulatory Authorities	Europe: Submit to regulatory authority per local reporting requirement.
Sponsor submit to:	
Investigator	All geographies: Submit as soon as possible, but no later than within 10 working days after the sponsor first learns of the event. (21 CFR 812.150(b)(1))
Regulatory authorities	US: Submit as soon as possible, but no later than within 10 working days after the sponsor first learns of the event. (21 CFR 812.150(b)(1)) Europe: Submit to regulatory authorities per local reporting requirement.
IRB/MEC	US: Submit as soon as possible, but no later than within 10 working days after the sponsor first learns of the event. (21 CFR 812.150(b)(1)) Europe: Submit to IRB/MEC per local reporting requirement
All other Adverse Events	
Investigator submit to:	
Medtronic	All geographies: Submit or report as required for local reporting requirements and protocol.
IRB/MEC	All geographies: Submit to IRB/MEC per local reporting requirements.
Regulatory authorities	All geographies: Submit to regulatory authority per local reporting requirement.
Sponsor submit to:	
Regulatory Authorities	All geographies: Submit to regulatory authority per local reporting requirement.
Device Deficiencies with SADE Potential	
Investigator submit to:	
Medtronic	All geographies: Submit or report as required for local reporting requirements and protocol.
IRB/MEC	All geographies: Submit to IRB/MEC per local reporting requirements.
Regulatory authorities	All geographies: Submit to regulatory authority per local reporting requirement.

Sponsor submit to:	
Regulatory Authorities	All geographies: Submit to regulatory authority per local reporting requirement.
All other Device Deficiencies	
Investigator submit to:	
Medtronic	All geographies: Submit in a timely manner after the investigator first learns of the event.
IRB/MEC	All geographies: Submit to IRB/MEC per local reporting requirements.
Regulatory authorities	All geographies: Submit to regulatory authority per local reporting requirement.

9.5 Subject death

9.5.1 Death Data Collection

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

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

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

9.5.2 Death Classification and Reporting

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

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

Sudden Cardiac Death (SCD): Natural death due to cardiac causes, indicated by abrupt loss of consciousness within one hour of the onset of acute symptoms; preexisting heart disease may have been known to be present, but the time and mode of death are unexpected. If time of onset cannot be determined, SCD will alternatively be defined as any unexpected cardiac death occurring out of the hospital or in the

emergency room as dead on arrival.

Non-sudden Cardiac Death: All cardiac deaths that are not classified as sudden deaths, including all cardiac deaths of hospitalized subjects on inotropic support.

Non-cardiac Death: A death not classified as a cardiac death.

Unknown Cardiac Classification: Unknown death classification is intended for use only when there is insufficient or inadequate information to classify the death.

The CEC will review deaths and provide a final adjudication of the cardiac classification.

9.6 CEC review

At regular intervals, an independent CEC will conduct a medical review of, at a minimum, all deaths and endpoint related events.

The CEC will consist of a minimum of three (3) non-Medtronic employed physicians that are not participating investigators for the study, including a CEC chairperson. At least two CEC members must adjudicate, at a minimum, all deaths and serious AEs related to any component of the systems under investigation. All other events may be adjudicated by at least one member of the CEC.

The CEC members may be blinded to the subjects' randomization assignment and/or other data or procedures that may influence their decision.

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

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

If the CEC disagrees with the investigator's classification of the event, the rationale will be provided to the investigator. If the investigator agrees with the CEC's adjudication, the CRF documenting the AE or AE update will be updated accordingly.

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

9.7 Adverse event classification

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

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

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

Table 10: Adverse event and subject death classification responsibilities

What is classified?	Who classifies?	Classification Parameters
Timing of the Event	Investigator	Pre-procedure, cryo-procedure, renal denervation-procedure, assessment, post-procedure
Relatedness	Investigator	Symplicity System, Arctic Front Cardiac Cryoablation System, renal artery denervation procedure, cryoablation procedure, Reveal LINQ system and procedure other procedures
	Sponsor	Same as Investigator
Severity	Investigator	SAE
	Sponsor	SAE, UADE, Complication or Observation (for all system or procedure related adverse events)
Diagnosis	Investigator	Based on presenting signs and symptoms and other supporting data
	Sponsor	MedDRA term assigned based on the data provided by investigator
Death Classification[1]	Investigator	Cardiac, Sudden Cardiac, Non-sudden Cardiac, Non-Cardiac, Unknown

[1]Deaths will only be adjudicated to death classification. All other adjudications information will be taken from the corresponding AE with an outcome of death

10. RISK ANALYSIS

Medtronic follows rigorous Quality Assurance and Control procedures throughout the life of a product, from the business analysis phase through development, market release, and post-market surveillance.

There are potential risks and side effects associated with these procedures. The investigator shall describe risks in further detail when asked by the subject. The current Instructions for Use document should be referenced as the list below may only be updated periodically during the course of the study.

Possible additional risks for participating in this study include the following (although others are possible):

- Mild skin discomfort or irritation-redness sensitivity of the skin cause during or after the procedures (e.g. electrodes used with the ECG and Holter recorder might cause mild skin discomfort or irritation or some skin discomfort following electrode removal or tape removal).
- Death-a complication or deterioration of health ultimately leading to a patient's death.
- Cardiopulmonary arrest-cessation of blood circulation and/or respiration due to dysfunction of the heart and/or lungs.
- Coronary artery spasm-constriction of a blood vessel.
- Heart rhythm disturbances/Arrhythmia-disruption of normal heart rate or rhythm, including bradycardia treated with atropine.
- Embolism-formation and dislodgement of a blood clot (thrombus) or dislodgement of cholesterol/plaque within the blood vessel, which travels downstream into small vessels, blocking blood flow and causing temporary or permanent damage to organs distal to blockage. Emboli are known to cause myocardial infarction, stroke or kidney damage, peripheral ischemia and may ultimately lead to incapacitation or death.
- Complications at catheter insertion site in the groin:
    - Pain-discomfort at the catheter insertion site that can range from mild to severe.
    - Hematoma/Bruising/Ecchymosis-a collection of blood in the tissue surrounding the catheter insertion site.
    - Pseudoaneurysm-a collection of blood in the tissue surrounding the catheter insertion site due to ongoing leaking of blood from a blood vessel.
    - AV fistula-an abnormal connection between an artery and a vein (i.e., cause by needle insertion through the femoral artery and vein).
    - Infection-localized redness, heat swelling and pain at the catheter insertion site.
    - Significant bleeding-blood loss from the catheter insertion site requiring surgery or transfusion of 2 or more units of packed red blood cells (PRBCs).

- Retroperitoneal bleeding-bleeding into the retroperitoneal space.
- Vascular complications requiring surgery-damage to an artery (e.g. femoral) or vein requiring surgical repair.
- Perforation of a blood vessel-unintended puncture through the wall of a blood vessel, such as a renal artery, requiring repair.
- Dissection of a blood vessel/pulmonary vein dissection-a tear within the wall of a blood vessel, which allows blood to separate the wall layers.
- Hypotension-low blood pressure.
- Hypertension-high blood pressure.
- Nausea-a sensation of unease and discomfort in the upper stomach with an urge to vomit.
- Vomiting-forceful expulsion of stomach contents through the mouth and/or nose.
- Pericardial effusion-fluid collecting in the sac that surrounds the heart.
- Cardiac tamponade-pressure on the heart as a result of fluid collecting in the sac surrounding the heart.
- Esophageal injury-damage to your swallowing tube
    - Atrio-esophageal fistula-abnormal passageway between the heart and esophagus.
- Phrenic nerve injury-damage to the nerve that controls breathing.
- Pulmonary vein stenosis-blockage in the blood vessels takes blood from the lungs to the heart.
- Endocarditis-inflammation of the inner surface of the heart.
- Infection (e.g. Pericarditis-inflammation of the sac that surrounds the heart, sepsis-infection throughout the body, urinary-infection of the urinary system).
- Pneumothorax-collapsed lung.
- Hemothorax-collection of blood around the lungs.
- Pleural effusion-collection of extra fluid around the lungs.
- Pneumonia-lung infection.
- Pulmonary edema-excess fluid in the lungs.
- Pulmonary hemorrhage-bleeding from the lungs.
- Injury to lung (e.g. bronchial lesion, bronchial constriction, bronchial fistula)
- Vagal nerve injury (e.g. Gastroparesis-delayed gastric emptying)
- Visual changed (e.g. blurred vision)
- Complications associated with contrast agents-adverse effects of contrast agents used during the procedure (e.g. allergic reaction or radio contrast nephropathy).
- Complications associated with medications commonly utilized during the

procedure-known risks of medications commonly used during the procedure (e.g. narcotics, anxiolytics, other pain medications, anti-vasospasm agents).

There are additional risks that could possibly be associated with the denervation procedure/therapy. These potential risks have not yet been quantified, but may include:

- Pain-discomfort that can range from mild to severe that may occur peri- and/or post-procedure.
- Damage to one or both kidneys and/or loss of kidney function-perforation of kidney or an occlusion or blood flow to the kidney (e.g. from stenosis or embolism) and/or reduction of glomerular filtration rate. If severe enough, this could require dialysis.
- Renal artery aneurysm-localized weakening and ballooning of the renal artery from the interventional procedure or the delivery of RF energy.
- Renal artery stenosis-narrowing of the renal artery due to the interventional procedure or the delivery of RF energy.
- Arterial spasm or constriction-acute or chronic narrowing of the renal artery lumen diameter at denervation locations due to arterial muscle contraction, local tissue contraction or local edema.
- Thermal injury to the vasculature or other structure from energy application- damage to an artery, vein or other structure due to the delivery of RF energy.
- Hypertension-worsening high blood pressure.
- Hypotension-low blood pressure. Blood pressure reduction may occur too far and/or too quickly and may cause end organ hypoperfusion.
- Orthostatic hypotension-temporary reduction of blood pressure when going from lying to standing, coupled with symptoms (e.g. dizziness, light headedness).
- Hematuria-blood in urine.
- Hemorrhage-significant blood loss.
- Proteinuria-elevated levels of protein in urine.
- Electrolyte disturbances-an imbalance of the electrolytes (sodium, potassium).
- Skin burn-damage to the skin caused by energy conduction via the ground pad used with the Symplicity Renal Denervation system (Symplicity Spyral Catheter and Symplicity G3 Generator).

There are additional risks that could possibly be associated with the Reveal LINQ.

- Rejection of the Reveal LINQ by your body, which may involve symptoms such as swelling, redness, or other irritation at, or near, the implant site.
- Movement of the Reveal LINQ from its initial position or coming through the skin.

- Infection at the site of the implant.
- Over-sensing or under-sensing (incorrectly identifying too many or too few) times where your heart may be showing a rhythm problem.

There are additional risks that could possibly be associated with the tests and procedures performed for this study. These potential risks are described below.

There are risks related to the blood tests required for the trial [e.g., excessive bleeding, fainting or light headedness, hematoma (bruising), infection, or the requirement of multiple punctures to locate a vein to draw the sample].

The cryoablation and renal artery denervation involve exposure to a small amount of radiation as part of the fluoroscopy procedure. Possible risks associated with this are:

- Increased risk of cancer and damage to the fetus of pregnant women.
- Increased radiation exposure time if an additional ablation procedure is necessary.
- Radiation injury resulting in skin inflammation and redness.

There are risks of undergoing CT scan, Renal Angiography and chest x-rays. These include: medication patches that can cause a skin burn and allergic reaction to the contrast material (if used) and exposure to radiation.

There is a possibility of risks to an unborn child. These risks are unknown. Women who are pregnant or expect to become pregnant during the course of the study are excluded from participating.

This study may involve unknown or unforeseen side effects or complications other than those mentioned above. If the above complications occur, they may lead to repeat or prolonged hospitalization, repeat procedures, emergency surgery, other emergency procedures or in rare cases, death.

10.1 Risk minimization

The potential risks associated with these therapies were identified and have been successfully mitigated. Any potential risks associated with this study are further minimized by to following ways:

- Selecting qualified investigators and training study personnel on the CIP.
- Investigators and center staff will receive appropriate training prior to any study procedures.
    - The sponsor has also attempted to minimize risk to subjects implementing a Data Monitoring Committee to review safety issues as part of the study. Investigators will be actively involved in the procedures and follow-up of the subjects undergoing these therapies. After treatment, subjects in the Symplicity AF clinical study will be followed at regular intervals to monitor the condition of their treatment and to assess any adverse events.
    - Risks will be minimized by careful assessment of each subject prior to, during, and after procedures. Prior to treatment, it is recommended subjects undergo a complete cardiac evaluation.
    - Medtronic has further minimized the possibility of risks by: implementing

quality control measures into production processes, providing guidelines for subject selection and evaluation, and providing adequate instructions and labeling.

10.2 Potential benefits

Although no assurances or guarantees can be made, there is reasonable expectation that adding the renal denervation procedure to pulmonary vein isolation to treat paroxysmal and persistent AF may be beneficial to the subject. Treatment with this system may reduce the sympathetic nerve activity to and from the kidneys, and cause a reduction in blood pressure. Evidence in the literature suggests that reduction of efferent sympathetic nerve activity to the kidney can a) cause relief of renal vasoconstriction, resulting in improved kidney function; b) reduce sodium retention, which can improve the clinical condition of patients with medical problems related to excess salt and water; and c) reduce the release of renin-a renal produced hormone which is often elevated in patients with either severe hypertension or heart failure. Interference of afferent sympathetic nerve activity from the kidneys can reduce central sympathetic activity, also causing reduction of blood pressure.[18,19,20]

The information gained from this study could result in the improved management of paroxysmal and persistent AF. Additionally, information collected from this study may assist in the design of new product(s)/therapy(ies) and/or indications for use.

11. PLANNED STUDY CLOSURE, EARLY TERMINATION OF STUDY OR STUDY SUSPENSION

11.1 Planned study closure

Study Closure is a process initiated by distribution of an initial study closure letter. Study closure is defined as closure of a clinical study that occurs when Medtronic and/or regulatory requirements have been satisfied per the CIP 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/MEC oversight is required until the overall study closure process is complete.

11.2 Early termination or suspension

Early Termination of the Study is the closure of the clinical study that occurs prior to meeting defined endpoints. This is possible for the whole study or a single center. Study Suspension is a temporary postponement of study activities related to enrollment and distribution of the product. This is possible for the whole study or a single center.

11.2.1 Study-Wide Termination or Suspension

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

- Adverse events associated with the system or product under investigation which might endanger the safety or welfare of the subject
- Observed/suspected performance different from the product's design intent

- Decision by Medtronic or regulatory body
- Recommendation of early termination by the DMC
- Technical issues during the manufacturing process or with the systems

11.2.2 Investigator/Center Termination or Suspension

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

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

11.3 Procedures for termination or suspension

11.3.1 Medtronic-Initiated

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

11.3.2 Investigator-Initiated

- The investigator will inform Medtronic and provide a detailed written explanation of the termination or suspension
- The investigator will promptly inform the institution
- The investigator will promptly inform the IRB/MEC
- The investigator will promptly inform the subjects and/or the personal physician of the subjects to ensure appropriate care and follow-up is provided
- In the case of a study suspension, subjects enrolled should continue to be followed out of consideration of their safety, rights and welfare

11.3.3 IRB/MEC-Initiated

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

12. STATISTICAL METHODS AND DATA ANALYSIS

Statisticians employed by Medtronic or their designees will perform the statistical analyses described in this section.

12.1 Sample size determination

The overall study sample size is 70 randomized subjects that undergo a pulmonary vein isolation procedure which is the required sample size for the primary effectiveness objective.

Subjects that are enrolled in the study may not go on to be randomized due to a variety of reasons, including elective withdrawal prior to randomization, blood pressure measurements that do not meet study criteria, or renal anatomy that is found to be ineligible upon angiography. Based on the rate of randomization among enrolled subjects in trials with similar screening criteria, up to 245 subjects may need to be enrolled and undergo screening in order to ensure that 70 subjects are randomized. Subjects who are randomized and meet either of the following two conditions do not count toward the 70 subjects randomized:

- exit the study without undergoing a pulmonary vein isolation procedure
- subjects who are randomized to the treatment group and are found not to meet inclusion/exclusion criteria during the renal denervation procedure.

All objectives will be analyzed once the last randomized subject has completed the 6-month follow-up visit. In addition, the primary effectiveness objective will be analyzed during interim analyses. These interim analyses may be performed after 32 and 50 subjects have been randomized and completed their 6-month follow-up visit. If data are deemed to sufficiently characterize this study objective by the sponsor at one of these analyses, enrollment may be stopped. Analysis results will be included in the study report(s).

12.2 General considerations

A modified intention-to-treat analysis will be performed and will serve as the primary analysis for all objectives in this study. The modified intention-to-treat

cohort will include all randomized subjects that undergo a pulmonary vein isolation procedure (i.e. have a cryocatheter inserted). Patients that are randomized, and meet either of the following two conditions will not be included in this cohort:

- exit the study without undergoing a pulmonary vein isolation procedure
- subjects who are randomized to the treatment group and are found not to meet inclusion/exclusion criteria during the renal denervation procedure.

The Statistical Analysis Plan (SAP) will include a comprehensive description of the statistical methods and reports to be included in the final study report. Any change to the data analysis methods described in the CIP will require an amendment only if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the clinical study report.

12.3 Primary safety objective

The primary safety objective characterizes the rate of safety composite events (Table 11) within each of the two study arms and also characterizes the difference in the rates between study arms.

Safety Composite Events are events that are serious, occur within a specified time interval (see Table 11) starting when the subject undergoes the study pulmonary vein isolation procedure and meet the definition in Section 12.3.1. The CEC adjudication will be used to classify subjects for this endpoint.

Table 11: Safety composite events and onset intervals

Serious Adverse Event	Onset Interval
Death	1 month
End-stage renal disease	1 month
Significant embolic event	1 month
Renal artery perforation requiring intervention	1 month
Renal artery dissection requiring intervention	1 month
Vascular complications	1 month
Hospitalization for hypertensive crisis	1 month
New renal artery stenosis	6 months
Cardiac damage	1 month
Pulmonary vein stenosis	6 months
Atrio-esophageal fistula	6 months
Arrhythmia	1 month
Persistent phrenic nerve palsy	6 months

12.3.1 Event Definitions

12.3.1.1 End-stage renal disease defined as two or more eGFR measurements <15mL/min/1.73m2 at least 21 days apart and requiring dialysis for one or more of the following: volume management refractory to diuretics, hyperkalemia unmanageable by diet and diuretics, acidosis bicarbonate <18 unmanageable with HCO3 supplements, or symptoms of uremia,

nausea, vomiting.

12.3.1.2 Significant embolic event resulting in end-organ damage (e.g. kidney/bowel infarct, lower extremity ulceration or gangrene, stroke or doubling of serum creatinine confirmed by at least two measurements at least 21 days apart). Stroke is *defined as a) rapid onset of a focal or global neurological deficit with at least one of the following: change in level of consciousness, hemiplegia, hemiparesis, numbness or sensory loss affecting one side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke, b) duration of a focal or global neurological deficit ≥24 h; OR <24h, if therapeutic intervention(s) were performed (e.g. thrombolytic therapy or intracranial angioplasty);OR the neurological deficit results in death, c) no other readily identifiable non-stroke cause for the clinical presentation (e.g., brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influence), d) confirmation of the diagnosis by at least one of the following: neurology or neurosurgical specialist, neuroimaging procedure (MR or CT scan or cerebral angiography), lumbar puncture (i.e., spinal fluid analysis diagnostic or intracranial hemorrhage*).

12.3.1.3 Vascular complications (e.g. clinically significant groin hematoma, arteriovenous fistula, pseudoaneurysm, excessive bleeding) requiring surgical repair, interventional procedure, thrombin injection, or blood transfusion (requiring more than 2 units of packed red blood cells within any 24-hour period during the first 7 days post procedure).

12.3.1.4 Hypertensive crisis/emergency is defined as severely elevated blood pressure, usually higher than 180/110 mm Hg, together with progressive or impending target organ damage, requiring in-patient hospitalization and typically admission to the Intensive Care Unit (e.g., with parenteral IV antihypertensive medications), not related to confirmed non-adherence with medication.

12.3.1.5 New renal artery stenosis defined as >70%, confirmed by angiography.

12.3.1.6 Cardiac damage due to any cause except pulmonary vein stenosis or atrio-esophageal fistula and including MI [the presence of any one of the following criteria: 1-detection of ECG changes indicative of new ischemia (new ST-T changes or new LBBB) which persist for more than one hour; 2-development of new pathological Q waves on an ECG; 3-imaging evidence of new loss of viable myocardium or new regional wall motion abnormality].

12.3.1.7 Pulmonary vein stenosis defined as >75% reduction in diameter of the baseline pulmonary vein area on CT or MRI.

12.3.1.8 Atrio-esophageal fistula defined as a connection between the atrium and the lumen of the esophagus. Evidence supporting this diagnosis includes documentation of esophageal erosion combined with evidence of a fistulous connection to the atrium such as air emboli, an embolic event, or

direct observation at the time of surgical repair. A CT scan or MRI scan are the most common methods of documentation of an atrial-esophageal fistula.

12.3.1.9 Arrhythmia excludes atrial fibrillation and including creation of new arrhythmias and/or worsening of existing arrhythmias.

12.3.1.10 Persistent phrenic nerve palsy defined as absent phrenic nerve function as assessed by a sniff test or chest x-ray including inspiration/expiration films. Persistent is defined as lasting 6 months or longer, or lasting until the last known follow-up if the follow-up is less than 6 months.

12.3.2 Hypothesis

There is no hypothesis for this objective.

12.3.3 Performance Requirements

Given the exploratory nature of a feasibility study, there is no performance requirement for this objective. The rate of safety composite endpoints will be characterized by estimating the rate within each arm and estimating the difference in rate between arms. These event rate estimates will provide critical guidance for designing a possible subsequent pivotal study.

12.3.4 Rationale for Performance Criteria

This primary safety endpoint is a composite that combines the safety endpoints from current Medtronic hypertension and AF studies and is intended to include serious adverse events associated with either the renal artery denervation or cryoablation procedure.

The safety composite event rate in the STOP-AF trial was 3.1% with a one-sided upper 95% confidence bound of 6.3%. The safety composite event rate in subjects undergoing renal artery denervation using the first generation Symplicity system (Symplicity Catheter and G2 Generator) in the Symplicity HTN-3 trial 1.4% (one-sided upper 95% confidence bound of 2.9%).[16] If undergoing both pulmonary vein isolation and renal artery denervation procedures at once is as safe as undergoing each procedure separately, then the proportion of patients that would be expected to experience a composite safety event is approximately 4.5% (based on observed rates) to 9.2% (based on upper 95% confidence bounds).

A DMC will periodically review accumulating safety data for the study, including the rate of safety composite events within each study arm and the difference in the rate between study arms.

12.3.5 Analysis Methods

For computing the proportion of subjects in each arm that experience safety composite events, Kaplan-Meier methods will be used. Since all components of the safety composite event include events through 30 days and four components include events through 6 months post-procedure, there is the potential for some subjects having incompletely assessed safety composite outcomes should they discontinue study participation prior to 6 months of post-procedure follow-up.
Kaplan-Meier estimation uses the time that each subject is free from a safety composite event, defined from the date of procedure to the earliest date that an

event meeting one of the safety composite event component definitions occurs. For events that are typically confirmed at a clinic visit (e.g. renal artery stenosis confirmed with angiography), it can be difficult to determine the onset date exactly. Therefore, events whose onset date is equal to a follow-up visit date within the 6-month visit window will be treated as having occurred at 180 days post-procedure. All subjects that are event-free through a completed 6-month follow-up visit within the 6-month visit window will be censored at 180 days. Otherwise, a subject's event-free time will be from the date of procedure to the latest follow-up visit. Treating safety composite event dates and censoring dates that occur at 6-month visits within the 6-month visit window as occurring at exactly 180 days post-procedure prevents bias in the Kaplan-Meier 6-month estimate. The log-log transformation will be used to calculate a two-sided 95% confidence interval for the rate of safety composite events within each study arm.

The difference in event rate between arms will be estimated by the difference in Kaplan-Meier estimates at 6 months. A 95% confidence interval for the difference will be constructed by applying the delta method to the log-log transform of the difference in the Kaplan-Meier estimates.

12.3.6 Determination of Patients/Data for Analysis

All randomized subjects in the modified intention-to-treat cohort will be included in the analysis.

12.3.7 Sample Size

There are no sample size requirements for this objective.

12.4 Primary effectiveness objective

The primary effectiveness objective compares the rate of chronic treatment success between study arms. Chronic treatment success is freedom from chronic treatment failure. Therefore, comparing the rate of chronic treatment success is equivalent to comparing the risk of chronic treatment failure.

Chronic treatment failure is defined as the occurrence of either

1) a documented episode of AF recorded on Reveal LINQ
2) an intervention for AF

occurring after a blanked follow-up period of 90 days from the study treatment procedure. AF episodes and repeat ablations that occur within 90 days of the study treatment procedure will not constitute chronic treatment failure.

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

12.4.1 Hypothesis

The primary effectiveness objective will be assessed with the following hypothesis:

H_0: $h_{Control}(t) = h_{Treatment}(t)$ for all $t \leq T$ years H_A:
$h_{Control}(t) \neq h_{Treatment}(t)$ for some $t \leq T$ years

where h(t) is the hazard function (risk) of chronic treatment failure and T is the total study time.

12.4.2 Performance Requirements

If the hazard ratio for chronic treatment failure between the Treatment and Control only arms is less than one and the two-sided log-rank p-value is less than 0.05, it will be concluded that the pulmonary vein isolation and renal artery denervation procedure results in a higher rate of chronic treatment success.

Given the feasibility nature of this study and relatively small sample size, even if the pulmonary vein isolation and renal artery denervation procedure results in a clinically meaningful improvement in the rate of chronic treatment success (e.g. an absolute 10-15% higher chronic treatment success rate through 6 months), the log-rank test may not reach statistical significance ($p<0.05$).

This study is intended to provide data to support the design of a pivotal trial. The estimates of the chronic treatment success rate for each study arm can provide that data whether the log-rank test is statistically significant or not.

12.4.3 Rationale for Performance Criteria

In the STOP-AF trial, subjects randomized to receive cryoablation had a 6- month chronic treatment success rate of 75.0%. In the patient population of this feasibility study, including patients with either paroxysmal AF or persistent AF and with uncontrolled hypertension, the rate of chronic treatment success is expected to be lower. Also, use of intensive AF monitoring with the Reveal LINQ device has the potential to identify patients with recurrent AF that might not be detected with periodic trans-telephonic and Holter monitoring, as was performed in the STOP-AF trial, leading to a lower rate of chronic treatment success. In the treatment arm, the addition of the renal artery denervation procedure to the pulmonary vein isolation procedure for treatment of AF has the potential to increase the rate of chronic treatment success. While it's uncertain to what degree these factors may affect the rate of chronic treatment success, this feasibility study is designed to be able to identify a difference in chronic treatment success rate if the rate through 6 months is at least 75% in the Treatment arm and 50% in the Control arm through 6 months.

12.4.4 Analysis Methods

A log-rank test will be used to perform this hypothesis test. The log-rank test uses the time that each subject is free from chronic treatment failure, defined from the date of procedure to the date of chronic treatment failure, if it occurs, or latest of the following: a) the last follow-up visit date, or b) the last date on which AF was assessed, if chronic treatment failure does not occur during the subject's study follow-up. Subjects will be included through all available study follow-up.

In addition to the log-rank test, Kaplan-Meier curves will be used to estimate the rate of chronic treatment success. Cox proportional hazards regression will be used to estimate the hazard ratio and its 95% confidence interval between study arms.

12.4.5 Determination of Patients/Data for Analysis

All randomized subjects in the modified intention-to-treat cohort will be included in the analysis.

12.4.6 Sample Size

There will be at least 78% power to test this objective provided at least 70 subjects undergo randomization.

The sample size calculation is based on the following assumptions:

- 1:1 randomization
- Constant randomization rate over 16 months
- Last enrolled subject followed through 6 months post-procedure
- 50% chronic treatment success in the PVI only arm versus 75% in the Treatment arm (equivalent to a hazard ratio of 0.415) through 6 months post-procedure
- Constant hazard ratio over all follow-up
- Cumulative alpha of 0.05. Any planned interim analyses will be constructed so that the overall Type I error of the study is no greater than 0.05.
- Constant attrition (dropout) of 5% per 6 months

The sample size calculation was performed in PASS 2008 using the log-rank (Lakatos) procedure. Accounting for a study attrition rate of up to 5% per 6 months ensures that the study will maintain the planned power of 78% in case attrition is higher than expected (approximately 1% per 6 months).

12.5 Secondary objective

12.5.1 Single Procedure Chronic Treatment Success

The secondary effectiveness objective characterizes the rate of chronic treatment success in Treatment and Control arms in the subgroup of subjects that do not undergo an additional pulmonary vein ablation procedure during the 90-day blanked follow-up period.

12.5.2 Hypothesis

There is no hypothesis for this objective.

12.5.3 Performance Requirements

There is no performance requirement for this objective.

12.5.4 Analysis Methods

Kaplan-Meier curves will be used to estimate the rate of chronic treatment success for each study arm. Cox proportional hazards regression will be used to estimate the hazard ratio and its 95% confidence interval between study arms.

12.5.5 Determination of Patients/Data for Analysis

All randomized subjects in the modified intention-to-treat cohort that do not undergo a permissible repeat cryoablation will be included in the analysis.

12.6 Ancillary objectives

The ancillary objective endpoints below will be compared between study arms in order to further characterize the differences in outcomes between patients randomized to pulmonary vein isolation only to those randomized to pulmonary vein isolation and renal artery denervation. Mean, standard deviation, median, and range will be used as descriptive statistics for continuous variables and counts and proportions for categorical variables. An ANCOVA model will be used to compare the mean change in continuous variables from baseline to 6 months
between the study arms. The ANCOVA model will include change measurement (e.g. heart rate, blood pressure) from baseline to the 6-month follow-up visit as the response and study arm indicator and baseline measurement as covariates. For the symptoms ancillary objective, a logistic regression model will model presence of each symptom at 6 months as the response and study arm indicator and baseline presence of symptom as covariates. For the freedom from chronic treatment failure off anti-arrhythmic drugs objective, a log-rank test over all available follow-up will be performed. For the AF burden objective, the Mann- Whitney U test will be used to compare the AF burden between study arms. This non-parametric test is used rather than the Student's t-test since AF burden tends to have a skew distribution with many values near zero. The difference in AF burden will be characterized by the Hodges-Lehmann estimator, the median of all pairwise differences in AF burden between study arms.

- Office systolic and diastolic blood pressure at 6 months compared to baseline
- Heart rate at 6 months compared to baseline
- Procedural measures (total procedure time, cryoablation procedure time, renal artery denervation procedure time, ablation time, fluoroscopy time, dye usage)
- Symptoms at 6 months compared to baseline
- Freedom from chronic treatment failure and off Class I and III anti-arrhythmic drugs following the blanking period
- AF burden (percent of time in AF) over all follow-up after the blanking period

12.7 Subgroup analysis

To characterize the consistency of the estimated treatment effect across AF diagnoses (paroxysmal or persistent AF), a score test will be performed on the interaction term in a Cox proportional hazards regression with study arm indicator, AF diagnosis, and interaction between study arm and AF diagnosis as factors.
Similar sub-group analyses, assessing the interaction term in a regression model, will be performed for the secondary and ancillary objectives. In addition to the subgroup analysis by AF diagnosis, a subgroup analysis using the same methodology will be performed to characterize the consistency of the estimated treatment effect across patients who received touch-up ablations to complete the electrical isolation of one or more pulmonary veins with an RF catheter versus those whose pulmonary veins were treated only with cryoablation.

12.8 Interim analysis

Interim analyses will be performed.

Two interim analysis of the primary effectiveness objective may be performed after 32 and 50 subjects have been randomized and completed their 6-month follow-up visits, respectively. Both the sponsor and the DMC will assess the results of the interim analyses of the primary effectiveness objective and based on this assessment, the sponsor may decide to stop enrollment.

Time Point of Interim Analyses of the Primary Effectiveness Objective	Cumulative Alpha	Boundary*	Pass/Fail Primary Effectiveness Objective
After 32 subjects were randomized and completed their 6-month visit	0.01	0.01	If a two-sided p-value ≤ 0.01, in favor of the treatment group, then the study passed the primary effectiveness objective
After 50 subjects were randomized and completed their 6-month visit	0.015	0.008	If a two-sided p-value ≤ 0.008, in favor of the treatment group, then the study passed the primary effectiveness objective
Final Analysis: After 70 subjects were randomized and completed their 6-month visit	0.05	0.04	If a two-sided p-value ≤ 0.04, in favor of the treatment group, then the study passed the primary effectiveness objective

*Boundaries were calculated using EAST 6.4.1

In addition to reviewing the effectiveness data from the interim analyses, the DMC will be responsible for assessing the accumulating data on safety of the procedures during the study. The primary responsibility of the DMC is to safeguard the interests of study participants. The DMC also monitors the overall conduct of the clinical study. Further information regarding the DMC is found in Appendix C: Data Monitoring Committee.

12.9 Pooling of study centers for analysis

Data from study centers will be pooled for analysis. Descriptive statistics of endpoints may be performed for groups of centers based on regional criteria. However, no statistical analysis will be performed to test center variation for the primary effectiveness objective. The study is expected to be conducted at up to 12 centers located in the United States and up to three centers in Europe with a total of 70 randomized subjects in the modified-intent-to-treat cohort. Given the small sample size, a formal test of interaction between randomization group and center will likely not be powered to detect a statistically significant difference for the primary endpoint if one exists. Likewise, the small sample size may not allow the use of a model adjusting for center as a random effect.

12.10 Missing data

Sensitivity analyses will be conducted to assess the robustness of the primary analyses to missing data should the issue of missing data arise in the study. Sensitivity analyses include, but are not limited to, tipping point analyses.

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 and be consistent with these source documents, and any discrepancies shall be explained in writing.

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

14. WARRANTY/INSURANCE INFORMATION

Warranty information is provided in the product packaging. Additional copies are available upon request.

Insurance (US)
Medtronic Inc. maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable law and custom concerning specific insurance coverage. If required, a Clinical Trial Insurance statement/certificate will be provided to the IRB. The study is conducted in multiple countries, therefore, reimbursement and indemnification will be addressed on a country specific basis in the study documents and center Clinical Trial Agreements.

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

15. MONITORING

It is the responsibility of Medtronic to ensure proper monitoring of this clinical investigation per regulations. Trained Medtronic personnel or delegates appointed by Medtronic may perform study monitoring at the study center in order to ensure that the study is conducted in accordance with the CIP, the Clinical Trial Agreement, and applicable regulatory and local requirements. Medtronic, or delegates, must therefore be allowed access to the subjects' case histories (clinic and hospital records, and other source data/documentation) upon request as per the Consent

Form, Privacy Authorization, Research Authorization (where applicable) and Clinical Trial Agreement.

15.1 Monitoring visits

Frequency of monitoring visits will be based upon subject enrollment, duration of the study, study compliance, number of adverse events, findings from previous monitoring visits and any suspected inconsistency in data that requires investigation. Regulatory documents may be reviewed at each study center.

Monitoring for the study will be done in accordance to the Medtronic internal study monitoring plan.

Monitoring visits may be conducted periodically to assess center study progress, the investigator's adherence to the CIP, regulatory compliance including but not limited to IRB/MEC approval and review of the study, maintenance of records and reports, and review of source documents against subject CRFs (source verification).

When source data verification is performed, the monitor must have direct access to original source documentation or certified copies of the original source must be provided.

If electronic source documentation is used at the site, the site must provide to the monitor:

1) Direct access to the electronic medical record (e.g. the monitor is given a guest password to directly access the system) or
2) Direct access to the electronic medical record by reviewing alongside appropriate study staff (e.g. a research coordinator) or
3) Certified copies of the electronic medical record. The site shall provide adequate documentation to the monitor describing their process for providing complete and accurate certified copies for required source documentation.

The monitor shall verify that he/she has complete access to all original source documentation required for the study (e.g. the monitor does not have a lower level of access to the original source documentation than the research coordinator or Principal Investigator necessary for the study).

Monitors review center regulatory and study compliance by identifying findings of non-compliance and communicating those findings along with recommendations for preventative/corrective actions to center personnel. Monitors may work with study personnel to determine appropriate corrective action recommendations and to identify trends within the study or at a particular center.

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 CRFs, should be kept in the Investigator Center 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 the investigation is terminated.

- All correspondence between the IRB/MEC, sponsor, monitor, regulatory bodies and/or the investigator that pertains to the investigation, including required reports.
- Subject's case history records, including:
    - Signed and dated informed consent form signed by subject
    - Observations of adverse events and device deficiencies
    - Medical history
    - Procedure and follow-up data
    - Documentation of the dates and rationale for any deviation from the protocol
    - Electronically signed and dated CRFs
    - Device disposition records
- All approved versions of the CIP
- Report of Prior Investigations
- Executed Clinical Trial Agreement
- Curriculum vitae for each investigator
- Delegated task list
- IRB/MEC approval documentation. Written information that the investigator or other study staff, when a member of the IRB/MEC, did not participate in the approval process. IRB/MEC approval of the current version of the CIP and Informed Consent Form and acknowledgment of the Report of Prior Investigations.
- Study training records for center staff
- Financial disclosure
- Any other records that regulatory bodies require to be maintained
- Final Study Report including the statistical analysis
- Any other regulatory authority or required records

16.2 Investigator reports

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

Safety data investigator reporting requirements are listed in Section 9 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 12: Investigator reports

Report	Submit to	Description/Constraints
Withdrawal of IRB/MEC approval (either suspension or	Sponsor and Relevant Authorities	US: 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))* Europe: Report if required by local law.
Progress report	Sponsor and IRB/MEC	US: 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))*. Europe: Provide if required by local law or IRB/MEC.
Study deviations	Sponsor and IRB/MEC	US: 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))* Europe: 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.
Failure to obtain informed consent prior to investigational device use	Sponsor and IRB/MEC	US: 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))* Europe: Informed consent shall be obtained in writing and documented before a subject is enrolled into the clinical investigation.
Final report	Sponsor and IRB/MECs	All geographies: This report must be submitted within 3 months of study completion or termination of the investigation or the investigator's part of the investigation. *(21 CFR 812.150(a)(6))*
Other	IRB/MEC and FDA	US: 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))*

16.3 Sponsor records

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

- All correspondence which pertains to the investigation
- Investigational device traceability record containing model and serial 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
- Signed and dated Confidential Disclosure Agreements or documentation of a Master Agreement

- Executed Clinical Trial Agreements, financial disclosure, curriculum vitae of each investigator and delegated task list
- All signed and dated CRFs submitted by investigator, including reports of AEs, and device deficiencies, and CRF corrections
- Samples of informed consents, and other information provided to the subjects, including translations (if applicable)
- 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
- Names/contact addresses of monitors
- Statistical analyses and underlying supporting data
- Final Report of the clinical investigation
- The CIP, CRFs, Report of Prior Investigations and study related reports, and revisions
- Study training records for center personnel and Medtronic personnel involved in the study
- 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. In addition to the reports listed below, Medtronic shall, upon request of reviewing IRB/MEC and regulatory bodies, provide accurate, complete and current information about any aspect of the investigation. Safety data Medtronic reporting requirements are listed in Table 9 of the Adverse Event section.

Table 13: Sponsor reports

Report	Submit to	Description/Constraints
Withdrawal of IRB/MEC approval	Investigators, IRB/MEC, and FDA	US: Notification within five working days. *(21 CFR 812.150(b)(2))*
Premature termination or suspension of the clinical investigation	Investigators, IRB/MEC, Relevant authorities and Head of the Institution	Europe: Provide prompt notification of termination or suspension and reason(s). (ISO 14155:2011)
Withdrawal of FDA approval	Investigators and IRB/MEC	US: Notification within five working days. *(21 CFR 812.150(b)(3))*
Withdrawal of CA approval	Investigators, Head of Institution, IRB/MEC, and relevant authorities	Europe: Investigators, IRBs/MECs will be notified only if required by local laws or by the IRB/MEC.
Investigator List	FDA	US: Submit at 6-month intervals, a current list of the names and addresses of all investigators participating in the investigation. *(21 CFR 812.150(b)(4))*
Progress Reports	IRB/MEC and FDA	US: Progress reports will be submitted at least annually. *(21 CFR 812.150(b)(4)(5), 812.36(f)* Europe: This will be submitted to the IRB/MEC only if required by the IRB/MEC.

Report	Submit to	Description/Constraints
Recall and device disposition	Investigators, IRB/MEC and FDA	US: 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	US: Investigator's report will be submitted to FDA within five working days of notification. *(21 CFR 812.150(b)(8))*
Final report	Investigators, IRB/MEC and FDA	US: 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 IRB/MECs within six months after completion or termination of this study. *(21 CFR 812.150(b)(7))*
Study deviation	Investigators	US: 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. Europe: 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. Center specific study deviations will be submitted to Investigators periodically.
Other	IRB/MEC, FDA	US: Accurate, complete, and current information about any aspect of the clinical investigation. (21 CFR 812.150(b)(10))

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

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

APPENDIX A: DRAFT DATA COLLECTION ELEMENTS

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

APPENDIX B: PRELIMINARY PUBLICATION PLAN

Publications from the Symplicity AF will be handled according to the Clinical Investigation Plan, Medtronic procedures and as indicated in the Clinical Trial Agreement.

Publication Committee

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

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

Membership in the Publication Committee does not guarantee authorship. The committee will meet at regular intervals.

Management of Primary, Secondary and Ancillary Publications

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

An ancillary publication is any publication that does not address the study objectives identified in the Clinical Investigation Plan. They include publications proposed and developed by other Medtronic departments or entities, clinicians participating in this clinical study and clinicians not participating in this clinical study. The committee will work with Medtronic to ensure that requests do not present conflicts with other proposals, are not duplicative and to determine which ancillary publication proposals, if any, will be supported.

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

Criteria for Determining Authorship

Publications will adhere to authorship criteria defined by the International Committee of Medical Journal Editors (ICMJE, Uniform requirements for manuscripts submitted to biomedical journals, www.icmje.org). Individual authorship criteria defined by the target journal or conference will be followed when it differs from ICMJE criteria.

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

- Substantial contribution to conception and design, or acquisition of data, or analysis and interpretation of data
- Drafting the article or revising it critically for important intellectual content
- Final approval of the version to be published

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

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

Transparency

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

- a Final Report, describing the results of all objectives and analysis, will be distributed to all investigators and IRB/MECs
- registering and posting the study results on ClinicalTrials.gov based on the posting rules stipulated
- submitting for publication the primary study results after the study ends
- disclosing financial interests of the co-authors of publications according to the policies set forth by the corresponding journals and conferences
- making an individual centers study data accessible to the corresponding investigator after the completion of the study, if requested

APPENDIX C: DATA MONITORING COMMITTEE

Ongoing oversight for this study will be provided by an independent DMC. The DMC will have one statistician, and at least two physicians specializing in either cardiac ablation, renal denervation, managing atrial fibrillation and/or managing blood pressure. None of the DMC members are participating in the Symplicity AF study. A chairperson from among those members has been identified. A DMC charter has been approved by the members.

The DMC will be responsible for assessing the primary effectiveness data as well as accumulating data on safety of the procedures during the study. The DMC will be responsible for safeguarding the interests of study participants and for monitoring the overall conduct of the clinical study. To enhance the integrity of the study, the DMC may also formulate recommendations related to the selection, recruitment, and retention of subjects, their management, improvement of adherence to protocol-specified regimens and procedures for data management and quality control. The DMC may also provide recommendations for early termination of the study for the safety of study participants.

Analyses of the study objectives for review by the DMC will be performed by a Medtronic statistician other than the lead statistician for the study. The lead study statistician will be blinded to all DMC analyses of study objectives. The unblinded statisticians will keep results strictly confidential per the DMC charter during the study.

APPENDIX D: INFORMED CONSENT TEMPLATES

The informed consent template will be distributed under separate cover.

APPENDIX E: PARTICIPATING INVESTIGATORS, INSTITUTIONS AND IRB/MECS

A complete list of participating investigators, institutions and IRB/MECs where study activities will be conducted will be distributed under a separate cover when available.

APPENDIX F: LABELING

Labeling for all system components can be found with each package insert. The Symplicity Spyral Catheter and the Symplicity G3 Generator will be labeled investigational in the United States. Labeling of CE marked devices follows local language requirements.

The Arctic Front Advance, Arctic Front Advance Pro, Freezor *MAX* and the Reveal LINQ System will not be labeled as investigational in the United States. Commercially available product will be used for the study in all geographies.

APPENDIX G: BLOOD PRESSURE MEASUREMENT PROCEDURES

1. Office blood pressure

All office blood pressure (OBP) measurements must be taken with the automatic BP Monitor and printer provided by Medtronic.

All attempts should be made to measure the subjects BP within the same approximate timeframe of the day (i.e., morning, afternoon, or evening).

A. Arm selection
    1. With the subject prepped for “Preparation” section below, measure BP in each arm. Print and label each measure.
    2. Use the arm with the higher BP for screening measurements and all subsequent measurements. If there is a reason to use a particular arm, document the reason and use that arm for all measurements.

B. Preparation at all visits
    1. Confirm the subject has taken all indicated anti-hypertensive medications prior to the measurements.
    2. Ensure the Date and Time has been set on the automatic BP Monitor and confirm the printer, if available, is operational.
    3. Confirm the subject did not drink coffee or alcohol, smoke or exercise within 30 minutes prior to the measurement.
    4. Request the subject to use the bathroom prior to measurements (a full bladder can affect the reading).
    5. The subject should be seated comfortably with the back supported and the upper arm bared without constrictive clothing. The legs should not be crossed.
    6. Ensure the BP cuff is appropriately sized (see below) and the upper arm is supported at the level of the heart (e.g. resting on a table at the level of his/her heart).

Table 14: Cuff size chart

Cuff size*	Fits arm circumference of (inches)
Small	7-9
Medium	9-13
Large	13-17
Extra Large**	17-20

*Opt for the larger of the two sizes if a subject is on the border of two cuff sizes.
**Subjects requiring greater than an extra-large cuff size at time of the screening must be excluded from the study.

    7. Perform a “test” BP measure. Print (if available) and label the measure.
    8. Have the subject sit comfortable and quietly for 5 minutes, with back supported and feet flat on the ground (i.e. not on an exam table, legs not crossed).

C. Method for taking BP at all visits
    1. With subject prepped for “Preparation” section above and using arm selected at Screening, take at least three seated BP measurements in order to obtain the BP average.
        a. Wait at least 1 minute between each measurement. Ensure the BP monitor time clock is used for tracking the time intervals.
        b. Print (if available) and label after each measurement.
    2. Three consecutive, consistent seated BP measurements must be obtained for the BP average.
        a. If the lowest and highest systolic BP vales of 3 consecutive measurements are more than 15 mmHg apart, take one additional reading and average the last 3 consecutive measurements (measurements 2-4). If the measurements are still more than 15 mmHg apart, take one additional reading and average the last 3 consecutive measurements (measurements (3-5). If more than 15 mmHg apart, continue to the sixth and final measurement.
        b. If less than a 15 mmHg difference cannot be obtained after at least 6 documented measurements, a 20 mmHg difference will be acceptable.
        c. At Screening: if the lowest and highest systolic BP values for the readings are more than 20 mmHg apart after 6 measurements, the subject must be excluded from the study.
    3. Record the last 3 consecutive, consistent readings for the case report form (do not pick the “best” 3).

APPENDIX H: BIBLIOGRAPHY AND PRECLINICAL AND CLINICAL INVESTIGATIONS

A complete bibliography, summary of relevant literature, summary and results of preclinical testing and summary and results of previous clinical investigational is provided in the Report of Prior Investigations.

APPENDIX I: MODIFICATIONS TO THE CLINICAL INVESTIGATION PLAN

Table 15 summarizes modifications made from previous version of CIP to the current version of CIP.

Table 15: CIP change history

Version	Applicable Sections	Change	Rationale	Number of subject enrolled
1.0	Not applicable	Not applicable	First release	0
2.0	1.1	Added a possible proposed indication should Medtronic choose to study this further.	Per recommendation from FDA	0
2.0	1.2, 12.1, 12.4.6	Sample size updated to include attrition	Per recommendation from FDA	0
2.0	5.2	Updated inclusion criteria: Office-based systolic blood pressure of ≥150 mm Hg based on average of three blood pressure readings despite treatment with 2 or more antihypertensive medications of different classes (one of these must be a diuretic) at maximum tolerated dose, highest tolerated dose, or highest appropriate dose for the patient per Principal Investigator's best clinical judgment. The subject should be on a stable antihypertensive drug regimen with no changes for a minimum of 2 weeks prior to enrollment and expected to be maintained on that regimen for at least 6 months.	Per recommendation from FDA	0
2.0	5.1, 12.3	Change to primary safety objective to compare rate of safety composite between treatment and control subjects.	Per recommendation from FDA	0
2.0	12.5	Changed Secondary Objective to Single Procedure Chronic Treatment Success	Adding the new secondary was per recommendation from FDA. The previous secondary became the new primary safety objective.	0

Version	Applicable Sections	Change	Rationale	Number of subject enrolled
2.0	5.1, 12.6	Added two new ancillary objectives: • Freedom from atrial tachyarrhythmias (including AF, atrial flutter and atrial tachycardia) of 30 seconds or longer • Chronic treatment Success off Class I and III anti-arrhythmic drugs following the blanking period	Per recommendation from FDA	0
2.0	5.2.1	Defined drug refractory as: failed (drug is ineffective or patient is intolerant) at least one Class I or III anti-arrhythmic drug	Per recommendation from FDA	0
2.0	5.2.2, 6.4 (Table 4), 6.7	Added requirement for TEE and exclusion of subjects when indicated	Per recommendation from FDA	0
2.0	5.2.2	Added exclusion: NYHA Class IV heart failure with in the past 6 months	Per recommendation from FDA	0
2.0	5.2.2	Updated exclusion in include hyperaldosteronism: Pheochromocytoma, Cushing's Disease (adrenal insufficiency), coarctation of the aorta, untreated hyperthyroidism, primary hyperparathyroidism or hyperaldosteronism	Per recommendation from FDA	0
2.0	5.3, 6.11	Clarified randomization strategy and process	Per recommendation from FDA	0
2.0	5.4, 12.7, APPENDIX C	Clarified interim analysis plans and DMC responsibility	Per recommendation from FDA	0
2.0	6.4, 6.16.1, 6.16.2, 6.20	TTM: Weekly TTMs added between 90 days and 12 Months post ablation procedure Updated symptomatic TTM to start after blanking period concurrent with weekly TTMs	Per recommendation from FDA	0
2.0	6.8	Added additional detail concerning the cryoablation procedure, including Phrenic nerve monitoring, anti-coagulation, procedure steps, clarification of other ablations, clarification of procedure documentation.	Per recommendation from FDA	0
2.0	6.9, 6.14	Details on peri and post-procedural anticoagulation including target ACT.	Per recommendation from FDA	0

Version	Applicable Sections	Change	Rationale	Number of subject enrolled
2.0	6.15	Updated Follow-up visit windows to correct 18 and 24 months windows and add 30 month	Correction	0
2.0	10	Risk Analysis: added additional risks possible for the cryoablation procedure	Per recommendation from FDA	0
2.0	12.3	Added definitions to some of the safety composite events	Per recommendation from FDA	0
2.0	12.2, 12.6 Various	Typographical errors, omissions and clarifications	Clarity	0
3.0	1.1	Modified a possible proposed indication should Medtronic choose to study this further	Per recommendation from FDA	0
3.0	5.2.1	Inclusion criteria updated to include definition of full dose anti-hypertensive medication	Per recommendation from FDA	0
3.0	5.2.2	Removed adrenal insufficiency from the exclusion criteria	Per recommendation from FDA	0
3.0	6.6	Added definition of full dose of anti-hypertensive medication and stated it must be documented	Per recommendation from FDA	0
3.0	6.8.2	Added PVI endpoint definition: After one or more cryoapplications, each pulmonary vein should be minimally assessed for entrance block and, where assessable, exit block to demonstrate the endpoint of electrical isolation.	Per recommendation from FDA	0
3.0	6.8.5	Clarified that demonstrated electrical block is collected on the case report form	Per recommendation from FDA	0
3.0	6.14	Added post procedure anticoagulation instructions	Per recommendation from FDA	0
3.0	12.3	Removed definitions in Table 10 and added a new section that provides further details regarding the safety events	Per recommendation from FDA	0
3.0	12.6	Clarified the ancillary objective Freedom from atrial tachyarrhythmias (including AF, atrial flutter and atrial tachycardia) of 30 seconds or longer and off Class I and III anti-arrhythmic drugs following the blanking period	Per recommendation from FDA	0
4.0	6.6	Clarified definition of anti-hypertensive medication dosing	Correction	0
5.0	12.3.1.2, 12.3.1.8, 12.3.1.10	Clarified safety event definitions	Per recommendation from FDA	0

Version	Applicable Sections	Change	Rationale	Number of subject enrolled
6.0	1.1, 5.1.2, 5.2.1	Inclusion of patients with persistent AF	Characterize results along the AF disease continuum	0
6.0	1.2, 5.3, 6.9, 12.1, 12.4.6	Randomization will occur in a 1:1 ratio which decreased the sample size to 70 subjects and upper enrollment limit to 245 subjects. This adjustment decreased the total study duration.	Primary reason for 2:1 randomization was to collect additional safety data but strong safety results from the Symplicity HTN-3 study lowered the safety risk level	0
6.0	3.0, 6.13, 6.15, 6.17, 6.18, 6.22, 9	Included the Reveal LINQ device which replaced trans-telephonic monitors and holters for recurrent AF detection.	Reveal LINQ has been commercially launched in the United States, allows unique opportunity to continuously monitor for recurrent AF and collect AF burden	0
6.0	3.1, 5.2.2, 6.10, 6.12	Added the Symplicity Spyral catheter and Symplicity G3 Generator. The Symplicity catheter remains in the CIP as a backup catheter for unforeseen circumstances with Symplicity Spyral or generator.	Technology improvements with the next generation catheter	0
6.0	4	Elaborated on what is part of regulatory compliance	Clarification	0
6.0	5.2.1	Added inclusion criteria for home monitoring	New information	0
6.0	5.2.2	Clarified that subjects may have one repeat TEE.	Clarification	0
6.0	5.2.2	Removed loop recorders from exclusion criteria.	Removed because Reveal LINQ is allowed	0
6.0	6.2, 16.1, 16.3	Added Financial Disclosure requirement	Clarification	0
6.0	6.6	Clarified that dose, units, frequency is only required for anti-hypertensive medications	Clarification	0
6.0	6.7	Added a CT scan to screen for renal anatomy eligibility followed directly by randomization rather than screening for renal anatomy directly after the pulmonary vein isolation procedure.	Allows for more efficiency with planning of the renal denervation procedure.	0

Version	Applicable Sections	Change	Rationale	Number of subject enrolled
6.0	6.7, 6.17, 12.6	Changed trans-thoracic echocardiogram measurement to only left atrial volume index for subjects diagnosed persistent AF. The repeat trans-thoracic echocardiogram at 6 months was removed	Want to exclude subjects who are very far along the AF disease continuum so that the two groups, paroxysmal and persistent aren't too dissimilar Likelihood of seeing a meaningful difference six months post procedure did not warrant this objective	0
6.0	6.7, 6.17, 12.6	Removed quality of life questionnaire	Likelihood of seeing a meaningful difference six months post procedure did not warrant this objective	0
6.0	5.2.1, 6.7, 6.17, 12.6	Removed ambulatory blood pressure monitoring requirement and follow up visit measurements	Deemed not critical for this study based on HTN-3 results	0
6.0	6.14	Changed the definition of device deficiency	New information	0
6.0	6.17	Removed the 3 month follow up visit	Primary reason for the 3 month follow up visit was to address any potential safety issues with the renal artery denervation procedure, risk level has been lowered with recent results from the Symplicity HTN-3 study	0
6.0	6.18	Included System Modification instructions for the Reveal LINQ device	New information	0
6.0	6.20	Clarified criteria for permissible retreatments	Unnecessary restriction in this feasibility study	0
6.0	7	Added instructions for device disposition with the Arctic Front Advance catheter	Result of including the persistent AF population in the study	0
6.0	9	Clarified that only system related, procedure related, cardiovascular related and serious AEs will be collected rather than all AEs	Safety risk level has been lowered with recent results from the Symplicity HTN-3 study	0
6.0	9	Changed Adverse Events Adjudication Committee (AEAC) to Clinical Events Committee (CEC)	Clarification because the committee will review more than adverse events	0
6.0	9.1	Added chest pain to the unavoidable AE table	Reasonable expectation of occurrence	0

Version	Applicable Sections	Change	Rationale	Number of subject enrolled
6.0	9.3	Elaborated market-release reporting requirements	Clarification	0
6.0	10	Added risks associated with the Reveal LINQ device	New information	0
6.0	12.3.4	Updated performance criteria with recent Symplicity HTN-3 study results	New information from the Symplicity HTN-3 study	0
6.0	12.4	Updated primary effectiveness objective because of how events are collected with the Reveal LINQ device	Continuous AF detection which wasn't possible with Holter and TTM	0
6.0	12.6	Added AF burden to ancillary objectives	Reveal LINQ calculates daily AF burden which is of interest in this patient population	0
6.0	12.6	Removed freedom from atrial tachyarrhythmias ancillary objective	Reveal LINQ does not have the capability to discriminate all atrial arrhythmias without making tradeoffs on AF collection	0
6.0	12.7	Added subgroup analysis	A result of including persistent AF patients in the study	0
6.0	Appendix E	Included institutions and IRBs that are expected to participate in the study	New information	0
6.0	Appendix F	Clarified that commercially released Arctic Front Advance Cryoablation Systems will be used in the study and not relabeled as investigational	Clarification	0
7.0	3.0 and throughout	Removed reference to the first generation Symplicity catheter and RF Generator	Only the next generation Symplicity Spyral catheter and Symplicity G3 Generator will be used in the study	11
7.0	9.1	Removed chest pain from unavoidable AEs	Per FDA recommendation	11
7.0	12.7	Subgroup analysis group added for those who receive touch up RF vs. not.	Per FDA recommendation	11
8.0	Throughout	Added Arctic Front Advance ST	This device is approved for use in the United States	0
8.0	3.3	Added one sentence regarding the AF detection algorithm	Clarification	0
8.0	6.4	Added Role of the sponsor representative during study procedures and follow up visits	Clarification	0

Version	Applicable Sections	Change	Rationale	Number of subject enrolled
8.0	6.7	Removed outdated reference to a 3-month visit	Correction. Missed on prior revision when the 3-month visit was removed.	0
8.0	6.14	Subjects with existing Reveal LINQ devices may be enrolled	Clarification	0
8.0	6.17	Changed the visit window calculation to date of pulmonary vein isolation procedure	Clarification	0
8.0	10	Added two risks	Known risks reported in literature and field performance data	0
8.0	12.4	Added language stating the primary effectiveness objective analysis includes AF detected from Reveal LINQ	Clarification	0
8.0	Appendix E	Updated center information	New information	0
9.0	Throughout	Removed Arctic Front Advance ST	Business decision	0
9.0	6.23	Removed alternative sources to document AF recurrence.	Reveal LINQ is the only source for recurrent AF allowed per protocol	0
9.0	12.4	Removed ECG and Holter as contributing to the definition of treatment failure for document AF recurrence.	Reveal LINQ is the only source for recurrent AF allowed per protocol	0
10.0	1.2	Updated study duration	New information	Not applicable
10.0	5.2.1 and 6.8	Inclusion criteria for blood pressure was lowered	Supports a larger cohort of patients who continue to have increased sympathetic tone	Not applicable
10.0	5.2.1 and 6.7	Inclusion criteria for number of antihypertension medications was lowered	Supports a larger cohort of patients who have uncontrolled hypertension on one antihypertensive medication	Not applicable
10.0	5.2.1 and 6.7	Inclusion criteria for hypertension medication at maximum dose was removed	Supports a larger cohort of patients who are not on maximum antihypertensive medication dose: avoids medication adherence identified in this population	Not applicable
10.0	5.2.2	Removed exclusion criteria for a condition where manipulation of the catheter within the heart would be unsafe but retained the evaluation as a requirement to occur prior to the ablation procedure.	Generally not assessed at the Baseline exam because the ablation procedure date has not been scheduled	Not applicable
10.0	6.7	Removed discouragement to enroll subjects on amiodarone.	Changed because of enrollment barrier	Not applicable

Version	Applicable Sections	Change	Rationale	Number of subject enrolled
10.0	6.9	Removed the word sealed from the randomization envelops, envelops have a blinded code label.	Clarification	Not applicable
10.0	6.15	Added “labeling” to the end of the sentences starting with NOTE.	Inadvertently missed so complete text was added	Not applicable
10.0	9.3	Added “impairment to a body structure or a body function” to the bullet point that begins with A condition necessitating medical or surgical intervention to prevent permanent	Inadvertently missed so complete text was added	Not applicable
10.0	9.5.1	Reworded the first paragraph to align with the CRF name and noted that’s it should be a SAE that led to death.	Clarification	Not applicable
10.0	9.5.2	In the Unknown Cardiac Classification, corrected sufficient to insufficient	Typo	Not applicable
10.0	10	Added lung lesion and Gastroparesis	Known risks reported in literature and field performance data	New information
10.0	12.4.4	Changed day zero to date of procedure, not dated of randomization and revised assessment of time to event.	Clarification	Not applicable
10.0	Appendix C	A DMC charter has been written	New information	Not applicable
10.0	Appendix E	Updated center information	New information	Not applicable
11.0	5.2.1	The inclusion criteria for blood pressure and antihypertensive medications was modified to include: subjects whose antihypertensive drug regimen is not expected to change for at least 6 months, as determined by their referring cardiologist and/or the investigator	Safety consideration for those subjects with uncontrolled hypertension during the first 6 months post procedure	Not applicable
11.0	6.7	Included the requirement to collect medication purpose	Inadvertently removed during prior revisions	Not applicable
11.0	6.8	Subjects with an average of 3 systolic blood pressure measurements ≤ 140 mmHg may have a repeat blood pressure assessment. The last version of this CIP stated >140mmHg.	Typo	Not applicable
11.0	6.8	The TEE section was reworded to state: “Subjects noted to have left atrial thrombus on TEE will not undergo the procedure and will be exited from the study unless thrombus resolution is confirmed on a repeat TEE.”	Clarification	Not applicable

Version	Applicable Sections	Change	Rationale	Number of subject enrolled
12.0	5.2.1	The inclusion criteria for blood pressure and antihypertensive medications was modified to include: The subject should be on a stable antihypertensive drug regimen with no changes for a minimum of 2 weeks prior to enrollment and the antihypertensive drug regimen is not expected to change for at least 6 months, as determined by the subject's referring cardiologist and/or the investigator.	Clarification	17
13.0	Title Page / Table 1	Added European contacts	European expansion	Not applicable
13.0	Table 2	Added core lab information	New Information	Not applicable
13.0	Section 1	Added European device/study status information and expansion of 3 sites	Include additional European centers to aid enrollment rate	Not applicable
13.0	Section 1.2	Increased center randomization cap from 30% to 50%	Allow high enrolling sites to continue enrollment to meet overall enrollment target	Not applicable
13.0	Section 3	Added European information for system description and intended use	European expansion	Not applicable
13.0	Section 3.4	Added Achieve Advance™ as an additional system component	Newly approved device available for use	Not applicable
13.0	Section 4	Added European regulatory compliance information	European expansion	Not applicable
13.0	Section 4	Added explanation of requirements for revisions to the CIP	Clarification	Not applicable
13.0	Table 5	Switched order of CT Scan and Cryoablation Procedure to chronological order	Typo	Not applicable
13.0	Section 6.2	Added European center activation requirements	European expansion	Not applicable
13.0	Section 6.6	Added European patient informed consent process requirements	European expansion	Not applicable
13.0	Section 6.12	Removed statement "If the angiogram confirms anatomy eligibility, the subject will be randomized"	Typo- subject is randomized after CT scan	Not applicable
13.0	Section 6.17	Added additional follow up visit windows in Table 6	Study length increase	Not applicable
13.0	Section 7	Added European requirements for device storage, handling and traceability	European expansion	Not applicable

Version	Applicable Sections	Change	Rationale	Number of subject enrolled
13.0	Section 8	Added note that study deviations are not required if a subject misses a monthly LINQ manual interrogation	Nightly automatic transmissions can be reviewed for AF episodes	Not applicable
13.0	Section 9	Added European adverse event and device deficiency requirements	European expansion	Not applicable
13.0	Section 12	Added: subjects who are randomized to the treatment group and are found not to meet inclusion/exclusion criteria during the renal denervation procedure will not count toward the 70 subjects randomized and will be included in a modified intention-to-treat analysis	Clarification	Not applicable
13.0	Section 12.9	Added a section regarding method for pooling of study centers for analysis	Clarification	Not applicable
13.0	Section 14	Added insurance information	Clarification	Not applicable
13.0	Section 16	Added European requirements for required records and reports	European expansion	Not applicable
13.0	Appendix E	Participating investigators, institutions and IRB/MECs updated to current status	New Information	Not applicable
13.0	Appendix F	Added European labeling information	European expansion	Not applicable
13.0	Throughout	Added reference to medical ethics committee (MEC) and regulatory bodies throughout	European expansion	Not applicable
14.0	Throughout	Sponsor internal distribution only	Sponsor internal discussion	Not applicable
15.0	Table 1	Revised Study sponsors and contacts	Updated information	47
15.0	Section 5.2.2	Removed exclusion criteria for pacemakers and defibrillators	Supports a larger cohort of patients contributing to enrollment	47
15.0	Section 5.2.2 and 6.12	Added the maximum renal artery diameter acceptable for the exclusion criteria	Typo	47

Version	Applicable Sections	Change	Rationale	Number of subject enrolled
15.0	Section 6.5 and 6.18.2	Allow a CareLink transmission from the subject's home as a substitution for an in-office device interrogation	Clarification	47
15.0	Section 7.1 and 7.3	Changed pedal to switch	Typo	47
15.0	Section 7.2, Table 7 and Appendix F	Added Freezor MAX	Clarification	47
15.0	Section 10	Modified risks to align with the current Arctic Front Advance IFU and added that the current Arctic Front Advance IFU should be referenced with respect to the possible risks	Updated to reflect recently approved labeling for the commercialized device	47
15.0	Section 12.3	Added text to the Safety Composite Event definition	Clinical Events Committee clarification request	47
15.0	Appendix E	Participating investigators, institutions and IRB/MECs updated to current status	New Information	47
16.0	Table 1	Revised Study sponsors and contacts	Updated information	55
16.0	Table 2	Revised Study Core Labs	Updated information	55
16.0	Table 3	Revised Committee contact information	Clarification of Steering Committee	55
16.0	Section 1.2	Revised Study description	Updated expected total study duration and months of enrollment given time needed to reach required subject treatment numbers	55
16.0	Section 1.2	Revised Study description	Updated to include provisions for the conduct of interim analyses	55

Version	Applicable Sections	Change	Rationale	Number of subject enrolled
16.0	Section 2	Revised section to include recently published renal denervation study results	New information	55
16.0	Section 2	Included use of Arctic Front Advance Pro Cardiac Cryoablation Catheter	AFA Pro recently granted FDA approval and CE mark	55
16.0	Table 4	Added Model Number(s) for AFA Pro Cardiac Cryoablation Catheter	AFA Pro recently granted FDA approval and CE mark	55
16.0	Section 3.2	Included use of Arctic Front Advance Pro Cardiac Cryoablation Catheter	AFA Pro recently granted FDA approval and CE mark	55
16.0	Section 5.2.2	Reinstated prior exclusion criteria for pacemakers and defibrillators	Protocol required LINQ monitoring for recurrent AF is not recommended in subjects with implantable Medtronic pacemakers and defibrillators; CareLink monitor unable to distinguish specific device for pairing; to ensure all recurrent AF in this study is captured via LINQ, implanted pacemakers and defibrillators from varying manufacturers will not be allowed	55
16.0	Section 6.1	Included use of Arctic Front Advance Pro Cardiac Cryoablation Catheter	AFA Pro recently granted FDA approval and CE mark	55
16.0	Section 6.10	Included use of Arctic Front Advance Pro Cardiac Cryoablation Catheter	AFA Pro recently granted FDA approval and CE mark	55
16.0	Section 6.24	Revised Study exit to allow for exit of subject with Reveal LINQ battery reaching end of life after completing at least 6 months of study follow-up	Support study subject safety and study participation satisfaction by not requiring repeat LINQ implant when study objective data is available and additional implant not clinically warranted	55
16.0	Section 7.2 and Table 7	Included use of Arctic Front Advance Pro Cardiac Cryoablation Catheter	AFA Pro recently granted FDA approval and CE mark	55

Version	Applicable Sections	Change	Rationale	Number of subject enrolled
16.0	Section 12.1	Added clarification for objective analyses and timepoints for potential interim analyses	Clarification and new information	55
16.0	Section 12.4.6	Revised power and sample size calculation assumptions	Provide new information resulting from provisions to conduct potential interim analyses	55
16.0	Section 12.8	Included the conduct of interim analyses	Aid sponsor decisions for continuing study	55
16.0	Section 12.8	Table added to show timepoints at which interim analyses may be conducted	Provide information regarding the pass/fail of primary effectiveness objectives for each scenario	55
16.0	Section 12.8	Added clarification of DMC's role in reviewing effectiveness data	Revised to reflect the conduct of interim analyses and the review of effectiveness data by the DMC	55
16.0	Appendix C	Added clarification of DMC's role in reviewing effectiveness data	Revised to reflect DMC review of effectiveness data generated by the conduct of interim analyses	55
16.0	Appendix E; Table 14	Participating investigators, institutions and IRB/MECs updated to current status	New information	55
16.0	Appendix F	Included use of Arctic Front Advance Pro Cardiac Cryoablation Catheter	AFA Pro recently granted FDA approval and CE mark	55
17.0	Section 6.18	Added alternate Follow-up methods	To allow for extenuating circumstances, such as a global pandemic.	98
17.0	Table 1	Updated Study sponsors and contacts	Updated information	98
17.0	Section 3	Added MyCareLink Patient Monitor Model number 24952	24952 Model number is available on the market in Europe	98

17.0	Throughout Document	Minor administrative and formatting updates	Updated information	98
17.0	Throughout Document	Updated based on received FDA approval of Arctic Front Advance, Arctic Front Pro and Freezor MAX with the Persistent AF expanded indication for the treatment of drug refractory recurrent symptomatic paroxysmal and persistent atrial fibrillation (episode duration less than 6 months)	Updated information	98
17.0	APPENDIX E:	Removed PARTICIPATING INVESTIGATORS, INSTITUTIONS AND IRB/MECS list	A complete list of participating investigators, institutions and IRB/MECs where study activities will be conducted will be distributed under a separate cover	98
18.0	Section 6.18	Administrative update to remove the following sentence from the section 6.18. "Scheduled in-office follow-up visits". These alternative methods have no potential impact on patient safety, do not affect data integrity and do not introduce study bias.' This sentence was added in version 17.0 of the CIP which was not implemented prior to version 18.0.	Per recommendation from FDA	100

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