Symplicity AF Statistical Analysis Plan

Version 2.0

NCT02064764

Statistical Analysis Plan

Clinical Investigation Plan Title	Symplicity AF Clinical Investigation Plan
Clinical Investigation Plan Version	16 (23/MAY/2018)
Sponsor/Local Sponsor	Medtronic, United States 8200 Coral Sea Street NE Mounds View, MN U.S.A. 55112 1-800-328-2518
Document Version	16.0

Table of Contents

1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• Not Applicable, New Document	Brett Peterson, Sr. Statistician
2.0	• Added an interim analysis plan reflecting analyses after 32 and 50 enrolled patients.	Brian Van Dorn, Principal Statistician

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AF	Atrial Fibrillation
AE	Adverse Event
AV	Atrioventricular
CEC	Clinical Events Committee
CIP	Clinical Investigation Plan
CRF	Case Report Form (synonomous with eCRF)
CT	Computerized Tomography
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form (synonomous with CRF)
eGFR	Estimated Glomerular Filtration Rate
FMD	Fibromuscular Dysplasia
LBBB	Left Bundle Branch Block
MI	Myocardial Infarction
mITT	Modified Intention-To-Treat
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging
NYHA	New York Heart Association
PCI	Percutaneous Coronary Intervention
PCTA	Percutaneous Transluminal Angioplasty
PVI	Pulmonary Vein Isolation
RF	Radio Frequency

SAP	Statistical Analysis Plan
TIA	Transient Ischemic Attack
UADE	Unanticipated Adverse Device Effect

3. Introduction

Study Purpose

The purpose of the Symplicty AF 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 market released Arctic Front Advance™ Cardiac Cryoablation system and investigational Symplicity™ Renal Denervation system (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. The Arctic Front Advance Cardiac Cryoablation system is not approved in the United States for the treatment of persistent AF, therefore it is considered investigational in this patient population.

This feasibility 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.

A randomized design was selected to compare safety and effectiveness between subjects receiving both renal artery denervation and pulmonary vein isolation within one procedure (Treatment arm) and subjects receiving only pulmonary vein isolation (Control arm). The randomized design will help minimize biases and control for confounding factors between comparison groups. Subjects and center personnel will be blinded to the randomization assignment until after the pulmonary vein isolation procedure.

Statistical Analysis Plan Purpose

This Statistical Analysis Plan (SAP) documents, before data is analyzed, the planned analyses that will be included in the Symplicity AF final report. Additionally, reports and analysis created for the Data Monitoring Committee (DMC) will use this SAP for guidance. Analyses for Symplicity AF publications will not be limited to this SAP.

This plan does not limit the analysis that may be provided in reports or publications.

The Symplicity AF Clinical Investigation Plan (CIP) version 12, dated 24/JUN/2016, was used to develop the SAP. Version 16 of the CIP, dated 23/MAY/2018, was used to update the SAP, largely to reflect the inclusion of an interim analysis.

4. Study Objectives

Primary Objectives

1. Safety: The primary safety objective characterizes the rate of safety composite events within each of the two study arms and also characterizes the difference in the rates between study arms.
2. Effectiveness: The primary effectiveness objective compares the rate of chronic treatment success between study arms.

Secondary Objective

1. 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.

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.

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

5. Investigation Plan

5.1. Study Design Summary

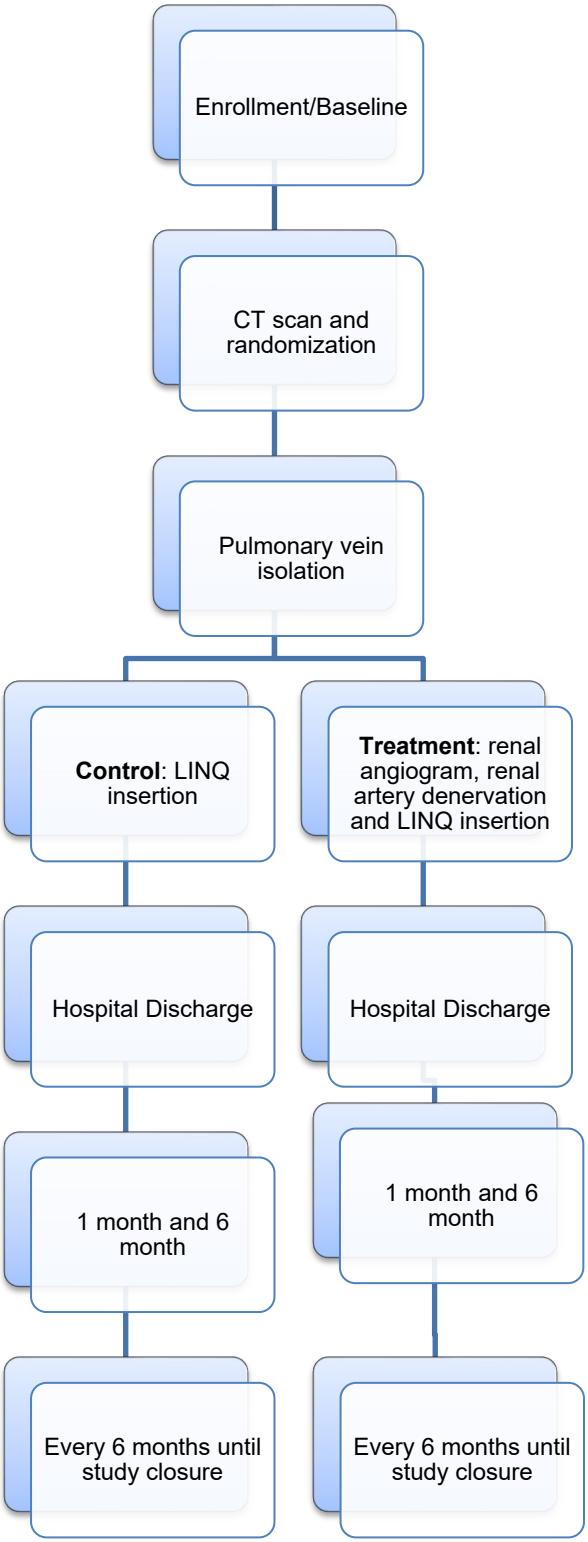
The Symplicity AF study is a prospective, randomized, multi-center, investigational, feasibility, clinical study. The study is expected to be conducted at up to 12 centers located in The United States. Up to 245 subjects will be enrolled in the study to ensure there are 70 randomized subjects. The number 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 30% (21) 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, if the study conducts a final analysis, 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. The figure below illustrates the study design.

Interim analyses of the primary effectiveness objective may 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.

Figure 1. Study Design Flowchart



Two interim analyses are planned. The first analysis will be conducted after 32 subjects are randomized and have completed their six-month visit. If the primary effectiveness objective is not passed after this analysis, the second will be conducted after 50 patients have been randomized and have completed their six-month visit. If neither interim analysis results in a successful primary effectiveness objective, the final analysis will be conducted once 70 patients are randomized and have completed their six-month visit.

5.2. Subject Selection Criteria

Subjects will be screened to ensure they meet all of the inclusion and none of the exclusion criteria. Institutional Review Board 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. 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. Randomization and Blinding

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. Subjects and center personnel will be blinded to the randomization assignment until after the pulmonary vein isolation procedure. Randomization envelopes may be returned to the randomization pool if the patient is exited before revealing the randomization assignment to center personnel. Crossing over to the Treatment group once assigned to the Control group is not allowed at any point during the study.

Medtronic statisticians are planning to conduct the analyses for this study. Analyses using actual randomization assignments will not be performed until after the final database freeze except for interim analyses or analyses performed for the DMC. Unblindings for the DMC will be considered planned unblindings. The freeze intended for the final report will also be considered a planned unblinding.

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.

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

More details can be found in the Symplicity AF Randomization and Blinding Plan document.

5.4. Interim Analyses

Two interim analyses are planned for the study. These analyses would 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.

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.

5.5. Endpoint Adjudication

An independent CEC will conduct a medical review of, at a minimum, all deaths and adverse events (AE). The CEC's adjudication will be used for data analysis.

5.6. Data Monitoring Committee

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 (i.e., the Primary Safety Objective).

6. Determination of Sample Size

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.

There will be at least 78% power to test the primary effectiveness objective provided at least 70 subjects undergo randomization and undergo a pulmonary vein isolation procedure. Table 1 below shows the expected incremental power at each analysis. The first and second look correspond to the interim analyses. The third interim look is the final analysis.

Table 1: Power at each stage of the analyses

Look	Patients w/ six month follow-up	Expected Incremental Power of Analysis
1	32	17.6%
2	50	10.1%
3	70	50.9%
	Cumulative Power:	**78.6%**

Subjects who are randomized and meet either of the following two conditions do not count toward the 70 randomized subjects to be used in the mITT set (define below):

- 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 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 Control arm (PVI only) 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
- Constant attrition (dropout) of 5% per 6 months

The original sample size calculation was performed in PASS 2008 using the log-rank (Lakatos) procedure. Updates to incorporate interim analyses were performed using EaST, version 6.4.1 with the survival module. 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).

A summary of the EaST output detailing the analyses is given on the following page.

Design: Survival Endpoint: Two-Sample Test - Parallel Design - Logrank Given Accrual Duration and Study Duration

Test Parameters	
Design ID	Des3
Design Type	Superiority
Number of Looks	3
Test Type	2-Sided
Specified α	0.05
Power	0.786
Model Parameters	
HR = λ_t/λ_c	
Under H0	1
Under H1	0.415
Ratio of % Surv. at Period #1:	1.5
Cum. % Surv. by Time =	6
Control (S_c)	50
Treatment (S_t)	75
Var (Log HR)	Null
Allocation Ratio (n_t/n_c)	1
Boundary Parameters	
Spacing of Looks	Unequal
Efficacy Boundary	Interp.
Accrual / Dropouts Parameters	
Cum % Accrued	100
Accrual Duration	16
Max Study Duration	22
Dropout	Yes

Variable Follow-Up Design: All subjects are followed until failure, drop out or end of study.

Sample sizes and events have been rounded.

Sample Size Information

	Control Arm	Treatment Arm	Total
Sample Size (n)			
Maximum	34	35	69
Expected H1	31.666	31.666	63.331
Expected H0	34.288	34.288	68.577
Events (s)			
Maximum	25	16	41
Expected H1	22.52	13.022	34.031
Expected H0	20.325	20.325	40.62
Dropouts (d)			
Maximum	2	3	5
Expected H1	1.723	2.547	4.27
Expected H0	1.985	1.985	3.97
Maximum Information (I):			10.25

Accrual and Study Duration

	Accrual Duration	Study Duration
Maximum	16	21.998
Expected H1	14.686	19.024
Expected H0	15.902	17.361

Stopping Boundaries: Look by Look

Look #	Info. Fraction (s/s_max)	Events (s)	Cumulative α Spent	Boundaries	
Efficacy Z					
Upper	Lower				
1	0.341	14	0.01	2.576	-2.576
2	0.463	19	0.015	2.611	-2.611
3	1	41	0.05	2.049	-2.049

Events, Sample Size, Dropouts, Pipeline and Analysis Times: Look by Look (Under H0)

Look #	Info. Fraction (s/s_max)	Sample Size (n)	Events (s)	Dropouts (d)	Pipeline (n-s-d)	Analysis Time	Boundary Crossing Prob (Incremental)
Efficacy							
Upper	Lower						
1	0.341	39	14	2	23	8.863	0.005
2	0.463	46	19	2	25	10.639	0.003
3	1	69	41	4	24	17.481	0.017

Events, Sample Size, Dropouts, Pipeline and Analysis Times: Look by Look (Under H1)

Look #	Info. Fraction (s/s_max)	Sample Size (n)	Events (s)	Dropouts (d)	Pipeline (n-s-d)	Analysis Time	Boundary Crossing Prob (Incremental)
Efficacy							
Upper	Lower						
1	0.341	46	14	2	30	10.492	1.216E-5
2	0.463	55	19	3	33	12.575	1.846E-6
3	1	69	41	5	23	21.998	5.177E-7

Dropout Information : Prob. of Dropout

Period #	By Time	Control	Treatment
1	6	0.05	0.05
2	12	0.1	0.1
3	18	0.15	0.15
4	22	0.183	0.183

7. Statistical Methods

7.1. Study Subjects

7.1.1. Disposition of Subjects

Subject disposition will be summarized in a CONSORT flow diagram similar to Figure 1. The number of subjects in each box of the figure will be reported, including the final number analyzed for the primary objective in each randomization arm. The reasons for subjects being removed from the primary objective analysis set will be reported in the flow diagram.

7.1.2. Clinical Investigation Plan Deviations

Deviations from the CIP are collected on an electronic Case Report Form (eCRF). A summary table of deviations will be reported using the Medtronic coding captured on the Medtronic Use Only eCRF. A listing of all deviations with typical and relevant details will be reported.

7.1.3. Analysis Sets

Cut-off dates will be applied to the study data when creating snapshots for study reporting. The analysis sets will be created from the applicable snapshot (e.g., for final report).

Enrolled

Patients who signed informed consent and met inclusion/exclusion criteria. Deviations and adverse events will be reported for all enrolled subjects. Enrolled subjects will be included in the CONSORT flow diagram.

Randomized

Enrolled subjects who are randomized.

Modified intent-to-treat

A modified intention-to-treat (mITT) analysis will be performed for the primary objectives. The mITT analysis set will include all randomized subjects that undergo a pulmonary vein isolation procedure (i.e. have a cryocatheter inserted). Patients that are randomized, but exit the study without undergoing a pulmonary vein isolation procedure will not be included in the mITT analysis set. Patients that are randomized to the treatment arm, but do not have the renal denervation procedure, will not be included in the mITT analysis set.

This analysis set is used for the following objectives described previously in Section 4:

- Primary safety

- Primary effectiveness
- Ancillary Objective 1
- Ancillary Objective 2
- Ancillary Objective 3
- Ancillary Objective 4
- Ancillary Objective 6

Secondary Objective

All subjects in the mITT cohort (i.e. subjects used for the Primary Effectiveness Objective) that do not undergo an additional pulmonary vein ablation procedure during the 90 day blanked follow-up period will be included the analysis of the secondary objective.

Ancillary Objective 5

The following subjects will be included in the analysis of ancillary objective 5:

- All subjects in the mITT cohort (i.e. subjects used for the Primary Effectiveness Objective) that do not undergo an additional pulmonary vein ablation procedure during the 90 day blanked follow-up period will be included this analysis

AND

- Have not used Class I and III anti-arrhythmic drugs following the blanking period

Case Report Form (CRF) data will be used to determine if subjects have or have not used Class I and III anti-arrhythmic drugs following the blanking period. If a subject has not used Class I anti-arrhythmic drugs and has not used Class III anti-arrhythmic drugs at all following the blanking period, then they will be used for this analysis. If a subject has used either Class I or Class III anti-arrhythmic drugs after the blanking period, then they will be excluded from this analysis.

7.2. General Methodology

Time to event methods will be used to analyze the primary objectives. The specific methods used for each analysis are given in the relevant sections within this SAP.

7.3. Center Pooling

Data from all centers will be pooled for analyzing all objectives. Adjustment for center effect will not be included in statistical modeling.

7.4. Handling of Missing Data and Dropouts

There are no plans for the imputation of any missing data. However, should the issue of missing data arise, sensitivity analyses will be conducted to assess the robustness of the primary analyses. Sensitivity

analyses include, but are not limited to tipping point analyses. Specifically for the tipping point analysis, subjects that are censored prior to the timepoint for which the survival estimate is being computed will be iteratively included as failures. For example, the earliest censored subject will be changed to a primary event (i.e., failure) at one day after their censor date. The analysis will be re-run and the estimate obtained. Then the next earliest censored subject will be changed to a primary event one day after their censor date, keeping the censored subjects already changed to primary events as primary events. The analysis will be re-run and the estimate obtained. This process will repeat until all censored subjects have been changed to primary events, such that all censored subjects will be counted as primary events in the last analysis run. Summaries of this process will be provided in order to illustrate which scenarios would and would not have resulted in success of the primary endpoint.

For subjects who are lost to follow-up, the time to event will be censored at the date the subject was last known to be free from the event when analyzing objectives with Kaplan-Meier or proportional hazards methods.

7.5. Adjustments for Multiple Comparisons

No alpha level adjustment for multiple comparisons will be made given the feasibility nature of this study.

7.6. Demographic and Other Baseline Characteristics

Information summarizing patient characteristics at baseline will be presented using descriptive statistics and tables for the mITT analysis set. Variables presented may include, but are not limited to, demographics, medical history, physical examination, NYHA classification, office blood pressure, arrhythmic symptoms, medications, and lab test results.

For quantitative variables, the mean, standard deviation, median, first quartile and third quartiles, minimum, and maximum will be presented based on non-missing values. For qualitative variables, counts and percentages will be given, using subjects with non-missing data as the denominator. The number of missing and non-missing values for each variable will be included.

The summary tables will include a column for mITT treatment arm subjects, mITT control arm subjects, and all mITT subjects.

Age will be computed using the variables AGE_YEARS and AGE_MONTH from the Baseline CRF: Age = AGE_YEARS + AGE_MONTHS/12

7.7. Treatment Characteristics

Procedural measure comparisons between study arms will be done in ancillary objective 3 (Section 7.10.6).

7.8. Interim Analyses

Two interim analyses are planned for the study. These analyses would 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. However, while there are formally defined stopping rules for a successful primary effectiveness endpoint, there are no stopping rules for futility.

Patients randomized to the trial who have not reached 6-months of follow-up are not considered in assessing the primary effectiveness objective.

The time points of the analyses and criteria for study success are given in Table 1 below:

Table 2: Timing and Success Criteria for Interim and Final analyses

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, using the Survival Module.

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.

7.9. Subgroup Analyses

Type I error will be 0.05 for subgroup analyses. These analyses will be performed after either a successful interim analysis or the final study analysis. Statistical comparisons are performed for exploratory purposes. No alpha level adjustment for multiple comparisons will be made.

AF diagnoses subgroups

To characterize the consistency of the estimated treatment effect across AF diagnoses (paroxysmal or persistent AF) from the primary effectiveness objective, 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 subgroup analyses, assessing the interaction

term in a statistical model, will be performed for the secondary objective and ancillary objectives #1, #2, #4, and #5.

The source data for defining AF diagnosis comes from Section C question 1 on the Baseline CRF. If paroxysmal atrial fibrillation is checked, then the subject is in the paroxysmal AF subgroup. If persistent AF is checked, then the subject is in the persistent AF subgroup.

Pulmonary vein isolation ablation subgroups (RF touch-ups or cryoablation only)

Additionally, 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. This subgroup analysis will be performed for the primary effectiveness objective, the secondary objective, and ancillary objectives #1, #2, #4, and #5.

The source data for defining touch-up ablations comes from questions on the Cardiac Cryoablation Procedure CRF and the Energy Applications CRF.

- Determine if a RF catheter was used at all during the procedure from Section D question 1 on the Cardiac Cryoablation Procedure CRF
    - Get the catheter number for each RF catheter used
- Determine which energy applications were done with the RF catheters from the Energy Applications CRF Section A (using the catheter number to match)
- If any of the energy applications using a RF catheter have one of the following locations, the subject is in the RF touch-ups subgroup; otherwise the subject is in the cryoablation only subgroup
    - LSPV, LIPV, LCPV, LMPV, RSPV, RIPV, RCPV, or RMPV

Subgroup methods for primary effectiveness and secondary objective

Kaplan-Meier curves will be used to estimate the rate of chronic treatment success in each subgroup with a 95% confidence interval. The main effects, interaction effects, confidence intervals, and p-values from each Cox proportional hazards regression will be reported using the score test.

Code similar to the following can be used for the Kaplan-Meier curves and estimates:

```
ODS graphics on ;
PROC LIFETEST DATA=survData conftype=loglog;
     By SubGroup;
     Plots = (survival(atrisk = 0 to <end time> by <interval time>)) ;
     STRATA trtGroup;
     TIME time*event(0);
RUN;
ODS graphics off ;
```

Code similar to the following can be used for the Cox proportional hazards model:

```
PROC PHREG DATA = survData;
      CLASS trtGroup subgroup;
      MODEL time*event(0) = trtGroup subgroup trtGroup*subgroup /
      TIES = efron;

RUN;
```

The subgroup variable designates what subgroup a given subject belongs to:

- AF Diagnosis
  - If AF diagnosis is paroxysmal, then subgroup equals 0
  - If AF diagnosis is persistent, then subgroup equals 1
- Touch-up ablations
  - If a subject does not receive a touch-up ablation, then subgroup equals 0
  - If a subject receives a touch-up ablation, then subgroup equals 1

Subgroup analysis methods for the ancillary objectives are described in their respective sub-sections in Section 7.10.

7.10. Evaluation of Objectives

7.10.1. Primary Safety

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

7.10.1.1. Hypothesis

There is no pre-specified hypothesis for this objective

7.10.1.2. Performance Criteria and Rationale

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 rates between arms. These event rate estimates will provide critical guidance for designing a possible subsequent pivotal study.

7.10.1.3. Endpoint Definition

The primary safety composite endpoint 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 endpoint for this objective is a Safety Composite Event 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. The adjudication source is the Medtronic Adverse Event CRF, Section C, question 1. The date of Safety Composite Events will come from the Adverse Event CRF.

Table 1. 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

Serious Adverse Event Definitions

- Death
- 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.
- 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 nonstroke 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).

- Renal artery perforation requiring intervention
- Renal artery dissection requiring intervention
- 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).
- Hospitalization for hypertensive crisis: 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.
- New renal artery stenosis defined as >70%, confirmed by angiography.
- Cardiac damage (due to any cause except pulmonary vein stenosis or atrio-esophageal fistula and including Myocardial Infarction (MI) (the presence of any one of the following criteria: 1-detection of electrocardiogram (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)).
- Pulmonary vein stenosis defined as >75% reduction in diameter of the baseline pulmonary vein area on CT or MRI.
- 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.
- Arrhythmia excludes atrial fibrillation and including creation of new arrhythmias and/or worsening of existing arrhythmias.
- 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.

7.10.1.4. 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 (time 0) 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 not counting them 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.

The confidence interval estimates the precision of the estimated difference in event rates between arms for the sample with a 95% confidence level. If the 95% confidence interval for the difference does not contain 0, we can conclude the event rates differ significantly between the Treatment and Control arms at a 5% significance level.

Code similar to the following can be used to obtain estimates in each treatment arm:

```
PROC LIFETEST DATA=survData conftype=loglog;
     STRATA trtGroup;
     TIME time*event(0);
     TEST trtGroup;
RUN;
```

Other code may be needed to analyze the difference in event rates between arms.

Explanation of variables

- trtGroup (treatment group):
    - Equals 1 if subject randomized to the treatment arm
    - Equals 0 if subject randomized to the control arm
- Event
    - Equals 1 if subject experienced a component of the primary safety endpoint during follow-up on or before the 6-month visit
    - Equals 0 if a subject did not experience a component of the primary safety endpoint during follow-up on or before the 6-month visit
- Time (from procedure date to first event or censor in days)
    - If Event = 1

- Determine the earliest date that a component of the primary safety endpoint was experience for each subject
    - If the earliest event onset date is equal to a follow-up visit date within the 6-month visit window, then Time equals 180 days
    - If the earliest event onset date is prior to the subjects 6-month visit window, then Time equals the earliest date that a component of the primary safety endpoint was experienced minus the date of procedure

- If Event = 0 (censor)
    - and the 6-month follow-up visit was completed within the 6-month visit window, then Time equals 180 days
    - and the 6-month follow-up visit was not completed, then Time equals the date of the latest visit prior to the 6-month visit minus the date of procedure

7.10.1.5. Datasets Analyzed

The mITT analysis set will be used for this objective.

7.10.1.6. Subgroup Analyses

Subgroup analyses are described in section 7.9.

7.10.2. Primary Effectiveness

The primary effectiveness objective compares the rate of chronic treatment success between study arms.

7.10.2.1. 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 at time t and T is the total study time. Hazard functions and survival functions are transformations of each other.

7.10.2.2. Performance Criteria and Rationale

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 (n=70 for the final analysis), 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.

Rationale for the performance criteria can be found in section 12.4.3 of the CIP.

7.10.2.3. Endpoint Definition

The endpoint for this objective is chronic treatment success. 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.

7.10.2.4. 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.

Code similar to the following can be used for the log-rank test and Kaplan-Meier curves:

```
ODS graphics on ;
PROC LIFETEST DATA=survData conftype=loglog;
     Plots = (survival(atrisk = 0 to <end time> by <interval time>)) ;
     STRATA trtGroup;
     TIME time*event(0);
     TEST trtGroup;
RUN;
ODS graphics off ;
```

Code similar to the following can be used for the Cox proportional hazards model:

```
PROC PHREG DATA = survData;
      CLASS trtGroup;
      MODEL time*event(0) = trtGroup / TIES = efron;
RUN;
```

7.10.2.5. Datasets Analyzed

The mITT analysis set will be used for this objective.

7.10.2.6. Subgroup Analyses

Subgroup analyses are described in section 7.9.

7.10.3. Secondary: Single Procedure Chronic Treatment Success

The secondary 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.

7.10.3.1. Hypothesis

There is no pre-specified hypothesis for this objective.

7.10.3.2. Performance Criteria and Rationale

There are no performance criteria for this objective.

7.10.3.3. Endpoint Definition

The endpoint for this objective is the primary effectiveness endpoint, chronic treatment success, as defined in section 7.10.2.3.

7.10.3.4. 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 for the treatment effect between study arms. To support this analysis, a log-rank test will be used to determine if the freedom from chronic treatment failure rate differs between arms.

The Kaplan-Meier curves use 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 on or after the 6-month follow-up.

7.10.3.5. Datasets Analyzed

The secondary objective analysis set will be used for this objective.

7.10.3.6. Subgroup Analyses

Subgroup analyses are described in section 7.9.

7.10.4. Ancillary #1: Office systolic and diastolic blood pressure at 6 months compared to baseline

Compare the difference of office systolic and diastolic blood pressure at 6 months and baseline between study arms.

7.10.4.1. Hypothesis

There is no pre-specified hypothesis for this objective.

7.10.4.2. Performance Criteria and Rationale

There are no performance criteria for this objective.

7.10.4.3. Endpoint Definition

The endpoints for this objective are defined as:

1) The difference in office systolic blood pressure in a given subject between the 6-month follow-up measurement and the baseline measurement
    a. For example: for subject 11111, the 6-month measure is 100 mm/Hg and the baseline measure is 80 mm/Hg so the endpoint value is 20 mm/Hg (100 minus 80).
    b. For example: for subject 22222, the 6-month measure is 70 mm/Hg and the baseline measure is 100 mm/Hg so the endpoint value is -30 mm/Hg (70 minus 100).

2) The difference in office diastolic blood pressure in a given subject between the 6-month follow-up measurement and the baseline measurement.
    a. Same logic as for systolic blood pressure.

7.10.4.4. Analysis Methods

Two ANCOVA models will be used, one to compare the mean change in office systolic blood pressure and one to compare the mean change in diastolic blood pressure from baseline to 6 months between the study arms after adjusting for the baseline measurement.

For change in office systolic blood pressure, the ANCOVA model will include the change measurement (as defined in 3.4.1.2) from baseline to the 6-month follow-up visit as the response and study arm indicator and baseline office systolic measurement as covariates.

For change in office diastolic blood pressure, the ANCOVA model will include the change measurement (as defined in 3.4.1.2) from baseline to the 6-month follow-up visit as the response and study arm indicator and baseline office diastolic measurement as covariates.

Code similar to the following can be used for the ANCOVA models:

```
PROC MIXED DATA = Data;
      CLASS trtGroup;
      MODEL change_measure = trtGroup baseline_measure;
RUN;
```

7.10.4.5. Datasets Analyzed

The mITT analysis set will be used for this objective.

7.10.4.6. Subgroup Analyses

The subgroups to be analyzed are defined in section 7.9. Two ANCOVA models will be constructed for each endpoint, one for each subgroup set; 1) AF diagnoses, and 2) pulmonary vein isolation. The models will include covariates for subgroup and the interaction between subgroup and treatment.

Code similar to the following can be used for the ANCOVA models:

```
PROC MIXED DATA = Data;
      CLASS trtGroup subgroup;
      MODEL change_measure = trtGroup subgroup trtGroup*subgroup
      baseline_measure;
RUN;
```

Example: In the AF diagnoses analysis, subgroup will equal 0 if AF diagnosis is paroxysmal and subgroup will equal 1 if AF diagnosis is persistent

7.10.5. Ancillary #2: Heart rate at 6 months compared to baseline

Compare the difference of heart rate at 6 months and baseline between study arms.

7.10.5.1. Hypothesis

There is no pre-specified hypothesis for this objective.

7.10.5.2. Performance Criteria and Rationale

There are no performance criteria for this objective.

7.10.5.3. Endpoint Definition

The endpoint for this objective is defined as the difference in heart rate in a given subject between the 6-month follow-up measurement and the baseline measurement

- For example: for subject 11111, the 6-month measure is 70 bpm and the baseline measure is 75 bpm so the endpoint value is -5 bpm (70 minus 75).

Source variables

- Baseline heart rate: VSORRES_HR from Baseline CRF Section E
- 6-month heart rate: VSORRES_HR from MONTH 6 FOLLOW UP CRF Section B

7.10.5.4. Analysis Methods

An ANCOVA model will be used to compare the mean change in heart rate from baseline to 6 months between the study arms after adjusting for baseline heart rate. The ANCOVA model will include the change measurement (as defined in 7.10.5.3) from baseline to the 6-month follow-up visit as the response and study arm indicator and baseline heart rate measurement as covariates.

Code similar to the following can be used for the ANCOVA models:

```
PROC MIXED DATA = Data;
      CLASS trtGroup;
      MODEL change_measure = trtGroup baseline_measure;
RUN;
```

7.10.5.5. Datasets Analyzed

The mITT analysis set will be used for this objective.

7.10.5.6. Subgroup Analyses

The subgroups to be analyzed are defined in section 7.9. Two ANCOVA models will be constructed, one for each subgroup set; 1) AF diagnoses, and 2) pulmonary vein isolation. The models will include covariates for subgroup and the interaction between subgroup and treatment.

Code similar to the following can be used for the ANCOVA models:

```
PROC MIXED DATA = Data;
      CLASS trtGroup subgroup;
      MODEL change_measure = trtGroup subgroup trtGroup*subgroup
      baseline_measure;
RUN;
```

7.10.6. Ancillary #3: Procedural measures

Compare procedural measures between study arms.

7.10.6.1. Hypothesis

There is no pre-specified hypothesis for this objective.

7.10.6.2. Performance Criteria and Rationale

There are no performance criteria for this objective.

7.10.6.3. Endpoint Definition

The following procedure measures endpoints will be reported for each study arm:

- total procedure time

    - Calculate total procedure time for each subject: Add cryoablation procedure time and renal artery denervation procedure time as defined below

- cryoablation procedure time
    - Start time: Time of first cryocatheter insertion (PROCTIME2 from CARDIAC CRYOABLATION PROCEDURE CRF Section C question 3)
    - End time: Time of last ablation catheter removal (PROCTIME5 from CARDIAC CRYOABLATION PROCEDURE CRF Section F question 2)
- renal artery denervation procedure time
    - Start time: Time of renal denervation catheter insertion (IMSTTM2 from RENAL DENERVATION PROCEDURE CRF Section C question 4)
    - End time: Time of renal denervation catheter removal (SPDUR1 from RENAL DENERVATION PROCEDURE CRF Section E question 3)
- ablation time
    - Cryoablation procedure
        - Sum of duration of each energy application (SEC) for a subject on the ENERGY APPLICATION CRF (unit of interest is a subject)
- fluoroscopy time
    - Cryoablation procedure
        - Elapsed fluoroscopy time at end of the cryoablation procedure (PROCTIME6)
- dye usage
    - Cryoablation procedure
        - Type of contrast used during procedure (IMP_GENERSED2)
        - Amount of contrast used (CONCERNTRATE1)
        - Concentration of contrast used (CONSERNTRATE2)
    - Renal artery denervation procedure
        - Type of contrast used during the procedure (SPORRESC)
        - Amount of contrast used (DPORRESN)
        - Concentration of contrast used (SPORRESN)

7.10.6.4. Analysis Methods

The procedure measure endpoints will be compared between study arms in order to further characterize the differences in outcomes between patients randomized to pulmonary vein isolation only and patients 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. T-tests will be used to test continuous endpoints between study arms. The Mann-Whitney test (a.k.a, Wilcoxon rank sum test) may be used if normality assumptions are not met. Fisher's exact test will be used to test categorical endpoints between study arms.

7.10.6.5. Datasets Analyzed

The mITT analysis set will be used for this objective.

7.10.6.6. Subgroup Analyses

No subgroup analyses are planned for this objective.

7.10.7. Ancillary #4: Symptoms at 6 months compared to baseline

Compare the presence of symptoms at 6 months between study arms.

7.10.7.1. Hypothesis

There is no pre-specified hypothesis for this objective.

7.10.7.2. Performance Criteria and Rationale

There are no performance criteria for this objective.

7.10.7.3. Endpoint Definition

The endpoints for this objective are presence of the following symptoms as recorded at the 6-month visit:

- Dizziness
- Palpitations
- Rapid heart beat
- Dyspnea
- Fatigue
- Syncope
- Other

7.10.7.4. Analysis Methods

A logistic regression model will be used with presence of each symptom at 6 months as the response and study arm indicator and baseline presence of symptom as covariates. An alpha of 0.05 will be used to

determine the significance of each covariate. Odds ratios and their corresponding 95% confidence intervals will be reported for each covariate to characterize their estimated effect on the response.

Code similar to the following can be used for the logistic regression models:

```
PROC LOGISTIC DATA = Data;
      CLASS trtGroup;
      MODEL Endpoint = trtGroup symptom_at_baseline / expb;
RUN;
```

7.10.7.5. Datasets Analyzed

The mITT analysis set, excluding subjects without the 6-month visit, will be used for this objective.

7.10.7.6. Subgroup Analyses

The subgroups to be analyzed are defined in section 7.9. A logistic regression model will be constructed each subgroup. The model will include covariates for subgroup and the interaction between subgroup and treatment.

Code similar to the following can be used for the logistic regression models:

```
PROC LOGISTIC DATA = Data;
      CLASS trtGroup subgroup;
      MODEL Endpoint = trtGroup symptom_at_baseline subgroup
      trtGroup*subgroup / expb;
RUN;
```

7.10.8. Ancillary #5: Freedom from chronic treatment failure and off Class I and III anti-arrhythmic drugs following the blanking period

Compare the rate of chronic treatment success (primary effectiveness endpoint) between study arms for subjects off of Class I and III anti-arrhythmic drugs following the blanking period.

7.10.8.1. Hypothesis

There is no pre-specified hypothesis for this objective.

7.10.8.2. Performance Criteria and Rationale

There are no performance criteria for this objective.

7.10.8.3. Endpoint Definition

The endpoint for this objective is the primary effectiveness endpoint, chronic treatment success, as defined in section 7.10.2.3.

7.10.8.4. Analysis Methods

Kaplan-Meier curves will be used to estimate the rate of freedom from chronic treatment failure for each study arm. The Kaplan-Meier curves use 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. A log-rank test will be used to determine if the freedom from chronic treatment failure rate differs between arms. An alpha of 0.05 will be used to determine statistical significance of the log-rank test.

Cox proportional hazards regression will be used to estimate the hazard ratio and its 95% confidence interval between study arms.

7.10.8.5. Datasets Analyzed

The following subjects will be included in this analysis:

- All subjects in the mITT analysis set that do not undergo an additional pulmonary vein ablation procedure during the 90 day blanked follow-up period will be included this analysis

AND

- Have not used Class I and III anti-arrhythmic drugs following the blanking period

Data from the Other Medication Log CRF will be used to determine if subjects have or have not used Class I and III anti-arrhythmic drugs following the blanking period. The log collects medication names which are classified as Class I or Class III anti-arrhythmic, etc. (SAS variable C_NAME). If a subject has not used Class I or III anti-arrhythmic drugs at all following the blanking period, all of their follow-up will be used for this analysis. If a subject has used either Class I or Class III anti-arrhythmic drugs after the blanking period, they will be excluded for this analysis.

7.10.8.6. Subgroup Analyses

Subgroup analyses are described in section 7.9.

7.10.9. Ancillary #6: AF burden over all follow-up after the blanking period

Compare the AF burden over all follow-up occurring after the blanking period between study arms.

7.10.9.1. Hypothesis

There is no pre-specified hypothesis for this objective.

7.10.9.2. Performance Criteria and Rationale

There are no performance criteria for this objective.

7.10.9.3. Endpoint Definition

The endpoint for this objective is the percent of time a subject is in AF over all of their follow-up after the blanking period.

Data obtained directly from the Reveal LINQ device will be used to calculate this endpoint in the following manner:

- Blanking period: 90 days after the cryoablation procedure
- Numerator: time in AF from Reveal LINQ device after the blanking period
    - Start date: Index cryoablation procedure date + 91
    - End date: End of follow-up time (latest date Reveal LINQ device data was recorded from study device data)
    - Numerator: The total amount of time (e.g., hours, days, etc.) the device shows the subject is in AF starting on the start date and ending on the end date
- Denominator: total follow-up time for a subject after the blanking period
    - Start date: Index cryoablation procedure date + 91
    - End date: End of follow-up time (latest date Reveal LINQ device data was recorded from study device data)
    - Denominator (days): End date – start date
    - Note: The denominator calculation assumes that the device will be monitoring for AF every day from when it is implanted to the latest date Reveal LINQ device data is recorded from the study device data. If it is possible that the device will not record 24 hours a day, 7 days a week, then we may need to use the device data to determine the total follow-up time where the device was monitoring for AF.
- Endpoint: (Numerator/Denominator) x 100

- Ensure time units for numerator and denominator are the same. The choice of denominator units will be made to most sensibly report the results, depending on how much time subjects are in AF (e.g., hours, days, etc.).

7.10.9.4. Analysis Methods

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 skewed 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. Pairs consist of one subject from each study arm. The pairwise difference is calculated by taking the difference of AF burden between the subjects in each pair. The total number of pairs is equal to the number of subjects receiving both renal artery denervation and pulmonary vein isolation within one procedure times the number of subjects receiving only pulmonary vein isolation.

The following will be reported:

- The median AF burden for each study arm
- Value of U statistic
- Number of subjects in each study arm analyzed for this objective
- Significance level (p-value from Mann-Whitney U test)
- Hodges-Lehmann estimator (estimates treatment effect)
- 95% confidence interval for Hodges-Lehmann estimator

7.10.9.5. Datasets Analyzed

The mITT analysis set will be used for this objective.

7.10.9.6. Subgroup Analyses

No subgroup analyses are planned for this objective.

7.11. Safety Evaluation

A summary table of AEs by classification the following classifications will be reported:

- Serious Adverse Events (SAE)
- Unanticipated Adverse Device Effects (UADE)
- Complication or observation
- Procedure relatedness
- System relatedness

A second table will be reported summarizing AEs by MedDRA preferred term.

The tables will show the counts of the number of a specified AE classification (e.g., SAE, MedDRA term, etc.) and the number of subjects who experienced the specified AE classification, and calculate the percentage of subjects who experience the specified AE classification.

A listing of all AEs will be reported with one row per AE.

All AEs for the enrolled analysis set will be included. The CEC classification of AEs will be used, except for SAEs and UADEs, where the Medtronic classification will be used since those are not adjudicated by the CEC.

Example summary table (the final validated version may differ)

Number of Events (Number, % Subjects)	Subjects Not Randomized (N = N_S)	Subjects Randomized (N = N_S)	Subjects Enrolled (N = N_S)
Total Adverse Events	**177 (116, 35.3%)**	**177 (116, 36.4%)**	**177 (116, 36.4%)**
Serious Adverse Event			
Yes	97 (66, 20.1%)	97 (66, 20.7%)	97 (66, 20.7%)
No	80 (64, 19.5%)	80 (64, 20.1%)	80 (64, 20.1%)
Unanticipated Adverse Device Effect			
Yes	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
No	177 (116, 35.3%)	177 (116, 36.4%)	177 (116, 36.4%)
Complication or Observation			
Complication	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Observation	177 (116, 35.3%)	177 (116, 36.4%)	177 (116, 36.4%)
Procedure Relatedness			
Related	49 (43, 13.1%)	49 (43, 13.5%)	49 (43, 13.5%)
Cryoablation	49 (43, 13.1%)	49 (43, 13.5%)	49 (43, 13.5%)
Repeat cryoablation	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Renal angiogram	N_E (N_S, %S)	N_E (N_S, %S)	N_E (N_S, %S)
Renal CT	N_E (N_S, %S)	N_E (N_S, %S)	N_E (N_S, %S)
Renal denervation	N_E (N_S, %S)	N_E (N_S, %S)	N_E (N_S, %S)
Reveal LINQ	N_E (N_S, %S)	N_E (N_S, %S)	N_E (N_S, %S)
Other	N_E (N_S, %S)	N_E (N_S, %S)	N_E (N_S, %S)
Not Related	126 (83, 25.2%)	126 (83, 26.0%)	126 (83, 26.0%)
Unknown	2 (2, 0.6%)	2 (2, 0.6%)	2 (2, 0.6%)

Number of Events (Number, % Subjects)	Subjects Not Randomized (N = N_S)	Subjects Randomized (N = N_S)	Subjects Enrolled (N = N_S)
Cryoablation	49 (43, 13.1%)	49 (43, 13.5%)	49 (43, 13.5%)
Repeat cryoablation	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Renal angiogram	N_E (N_S, $\%_S$)	N_E (N_S, $\%_S$)	N_E (N_S, $\%_S$)
Renal CT	N_E (N_S, $\%_S$)	N_E (N_S, $\%_S$)	N_E (N_S, $\%_S$)
Renal denervation	N_E (N_S, $\%_S$)	N_E (N_S, $\%_S$)	N_E (N_S, $\%_S$)
Reveal LINQ	N_E (N_S, $\%_S$)	N_E (N_S, $\%_S$)	N_E (N_S, $\%_S$)
Other	N_E (N_S, $\%_S$)	N_E (N_S, $\%_S$)	N_E (N_S, $\%_S$)
System Relatedness			
Related	14 (14, 4.3%)	14 (14, 4.4%)	14 (14, 4.4%)
Symplicity catheters	N_E (N_S, $\%_S$)	N_E (N_S, $\%_S$)	N_E (N_S, $\%_S$)
Symplicity radio frequency generator	N_E (N_S, $\%_S$)	N_E (N_S, $\%_S$)	N_E (N_S, $\%_S$)
Arctic Front Advance cardiac cryoablation catheter	N_E (N_S, $\%_S$)	N_E (N_S, $\%_S$)	N_E (N_S, $\%_S$)
Manual retraction kit	N_E (N_S, $\%_S$)	N_E (N_S, $\%_S$)	N_E (N_S, $\%_S$)
Freezor MAX cardiac cryoablation catheter	N_E (N_S, $\%_S$)	N_E (N_S, $\%_S$)	N_E (N_S, $\%_S$)
Medtronic CryoCath CryoConsole system	N_E (N_S, $\%_S$)	N_E (N_S, $\%_S$)	N_E (N_S, $\%_S$)
Flex Cath sheath	N_E (N_S, $\%_S$)	N_E (N_S, $\%_S$)	N_E (N_S, $\%_S$)
Achieve mapping catheter	N_E (N_S, $\%_S$)	N_E (N_S, $\%_S$)	N_E (N_S, $\%_S$)
Reveal LINQ system	N_E (N_S, $\%_S$)	N_E (N_S, $\%_S$)	N_E (N_S, $\%_S$)
Other system component	N_E (N_S, $\%_S$)	N_E (N_S, $\%_S$)	N_E (N_S, $\%_S$)
Not Related	159 (108, 32.8%)	159 (108, 33.9%)	159 (108, 33.9%)
Unknown	4 (4, 1.2%)	4 (4, 1.3%)	4 (4, 1.3%)

Example listing (the final validated version may differ)

Subject AE Number	MedDRA Preferred Term	Onset Date Procedure Date (Onset – Procedure Date)	Serious AE	UADE	Complication or Observation (CEC)	System/Procedure Relatedness (CEC)	AE Description	Diagnostic Tests/Procedures and Actions Taken	Outcome
M300006001 AE Number: 0	Hematoma	05FEB2014 Index Procedure Date: 03FEB2014 (2)	Yes	No	Observation	System: Not related Procedure: Unknown (Renal Angiogram)	femoral hematoma due to coronarography punction	Test or Procedure: None Action: None	Resolved (20FEB2014)

Subject AE Number	MedDRA Preferred Term	Onset Date Procedure Date (Onset – Procedure Date)	Serious AE	UADE	Complication or Observation (CEC)	System/Procedure Relatedness (CEC)	AE Description	Diagnostic Tests/Procedures and Actions Taken	Outcome
M300011004 AE Number: 1	Soft tissue mass	25JUN2014 Index Procedure Date: 01JUN2014 (24) Repeat Procedure Date: 25AUG2014	No	Yes	Complication	System: Flex Cath Sheath, Achiever Mapping Catheter Procedure: Cryoablation, Renal Angiogram, Renal CT	Prior to study enrollment pt fell off ladder on 25 June 2014 and was admitted to hospital. During trauma work up pt had full body CT scan with incidental findings of a discrete lung nodule and soft tissue mass in right adrenal gland. Radiologist review suggested masses are suspicious of metastasis from an unidentified primary malignancy. Pt attended study follow up on 01 Oct 2014 and informed study team of scheduled abdominal PET scan in very near future.Pt reports no symptoms related to masses.	Test or Procedure: 25JUN2014: CT Scan Results: R lung nodule and soft tissue mass on R adrenal gland. Action: 26JUN2014: Hospitalization 27JUN2014: Medications	Unresolved, further actions or treatment planned [Awaiting PET scan in near future.]

7.12. Health Outcomes Analyses

No health outcome analyses are defined in the CIP and thus none are planned for the final report.

7.13. Changes to Planned Analysis

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 CIP or this SAP, and the justification for making the change, will be described in the clinical study report.

The CIP states 'all randomized subjects will be included in the analysis' of some objectives (e.g., CIP section 12.4.5). This differs from CIP section 12.2 that states the mITT analysis set will serve as the primary analysis for all study objectives. The analysis sets for each objective as stated in this SAP will be used for the final report analyses.

8. Validation Requirements

Minimum validation requirements for the programs written to execute the analyses in this SAP:

- Primary objectives: Level I (independent program)
- Secondary objective: Level II (peer review)
- Ancillary objectives: Level II (peer review)

- AE tables and listings: Level II (peer review)
- Deviation table and listing: Level II (peer review)
- CONSORT diagram numbers: Level II (peer review)
- Other programs needed for final report analyses not specified: Level II (peer review)

Programs previously validated at Level I or Level II further modified with minor changes may be validated at Level III.

It is expected that Standard Operating Procedures will be followed for other programs that effect the programs written to execute the analyses in this SAP, such as data retrieval programs, dataset mapping programs, analysis dataset programs, etc.