VICTORY AF
Evaluation of Multielectrode Phased RF Technology in Persistent Atrial Fibrillation
Statistical Analysis Plan Version 2.0
18 July 2013
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Medtronic

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VICTORY AF

Evaluation of Multi**elec**trode Phased **R**F Technolog**y** in Persistent **A**trial **F**ibrillation

Statistical Analysis Plan

Version 2
18 July 2013

Document Change History			
Version	Version Date	Description of and Rationale for Change	Effects on Other Documents
1	28 March 2013	Initial Release	NA
2	18 July 2013	• Updated to align with version 5 of the VICTORY AF clinical investigational plan • Added subgroup analysis by PVAC catheter type if more than one PVAC model is used during study • Clarified that "at least one Phased RF catheter deployed into the left atrium" means that a Phased RF catheter is placed in the left atrium and Phased RF energy is delivered • Corrected grammatical and typographical errors	None

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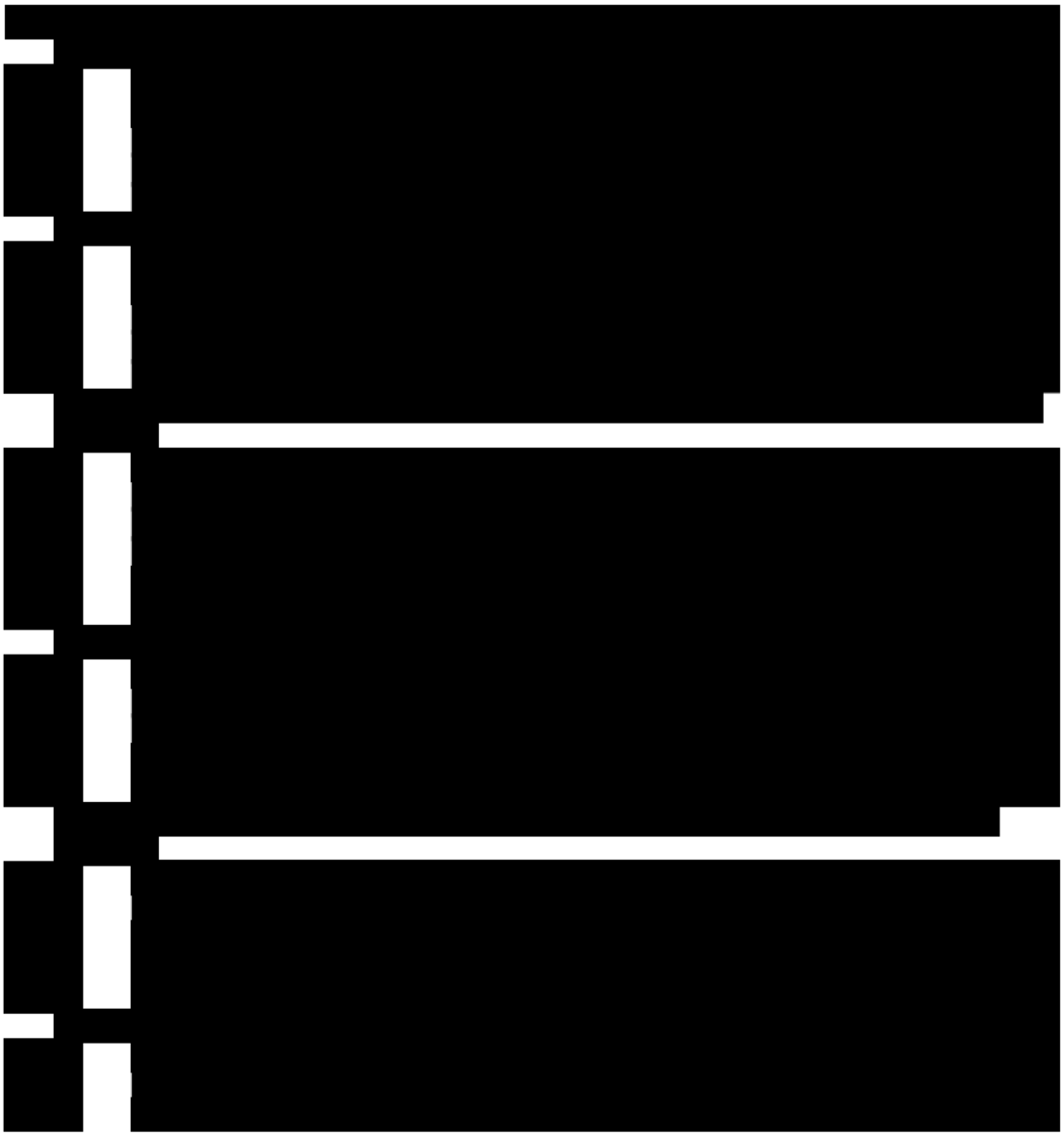

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1 PURPOSE

This Statistical Analysis Plan (SAP) has been designed to document, before data is analyzed, the rationale for the VICTORY AF study design, and the planned analyses that will be included in the pre-market approval (PMA) and final study reports.

2 RATIONALE FOR STUDY DESIGN

VICTORY AF is a prospective, global, multi-center, single arm clinical study. The purpose of this clinical study is to evaluate the risk of procedure and/or device related strokes in subjects with persistent or long-standing persistent atrial fibrillation (AF) undergoing ablation with the Phased RF system. The study design, objectives, and analytical methods have been developed with close consultation with the US Food and Drug Administration (FDA) during the pre-IDE process.

2.1 Study Purpose

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

2.2 Study Scope

The study is expected to be conducted at approximately 40 centers located in Europe, Canada and the United States. A maximum of 350 subjects will be enrolled in the study to ensure 300 subjects can be evaluated for the primary safety endpoint. Subjects will be followed for 30 days post reablation (if reablation required) procedure or 6 months post index procedure (if no reablation procedure required) for the primary safety objective. The primary safety objective will be evaluated after at least 300 ablated subjects complete the 30 day post index or reablation procedure visit and have had the opportunity for a reablation. Alternatively, the study may stop early for futility prior to completing enrollment if more than 6 procedure and/or device related strokes occur within the 30 day peri-procedural period.

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

2.3 Background and Justification

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

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

2.4 System Description

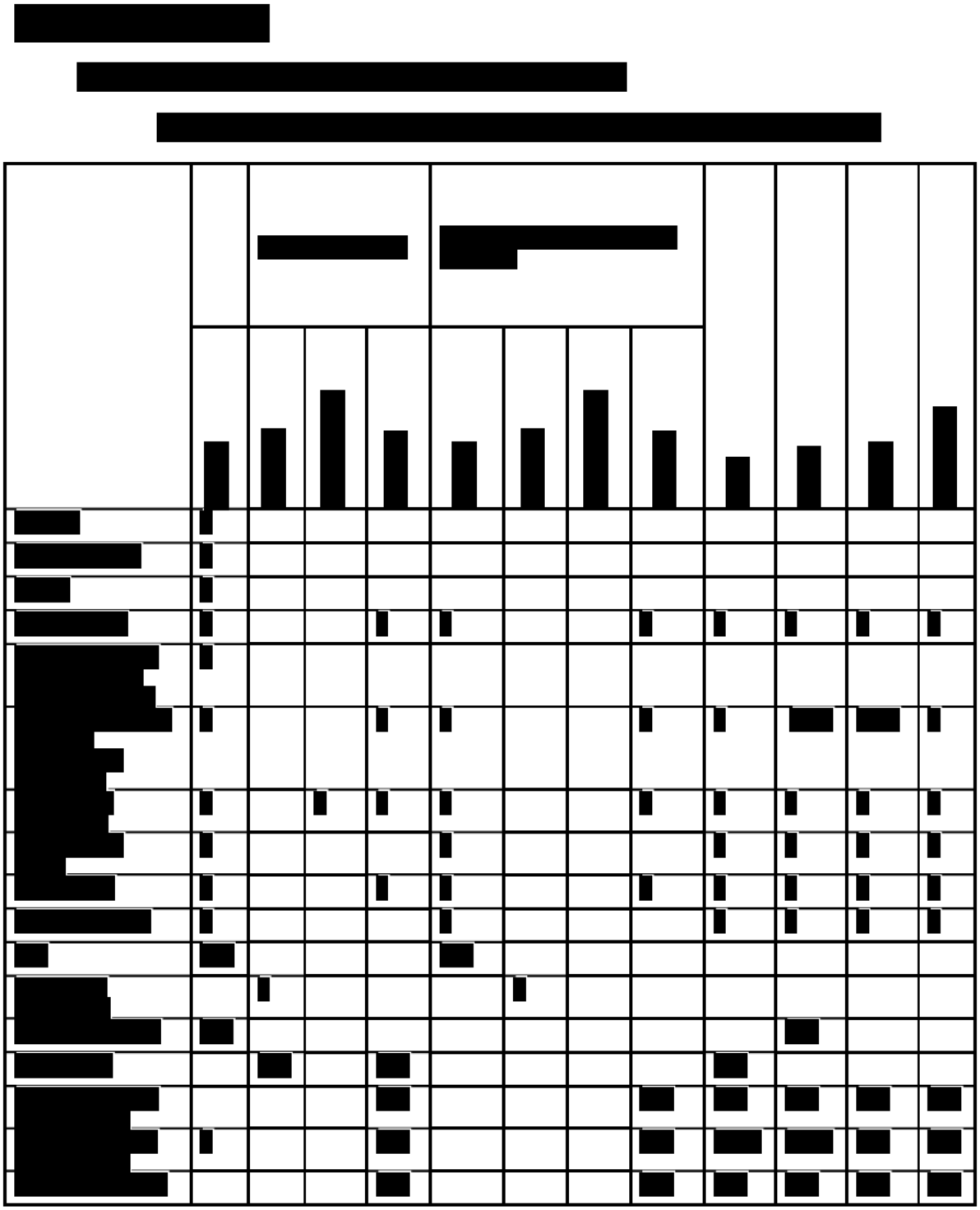
The Medtronic Phased RF System is intended to be used for mapping intracardiac electrograms and to deliver precise, temperature controlled radio frequency (RF) ablation therapy within the atria of the heart for the treatment of atrial fibrillation. The main components of the System are listed in Table 1.

Table 1: System Component Information

Component	Investigational or Market-released
Multi-Channel RF Ablation Generator	Investigational (US Only)
Catheter Interface Cable	Investigational (US Only)
Multi-Array Septal Catheter (MASC)	Investigational (US and Canada Only)
Multi-Array Ablation Catheter (MAAC)	Investigational (US and Canada Only)
Pulmonary Vein Ablation Catheter (PVAC)	Investigational (US Only)
Pulmonary Vein Ablation Catheter (PVAC GOLD)	Investigational (US and Canada** Only)
ECG Interface Box	Investigational (US Only)
ECG Interface Box Cable	Investigational (US Only)
ECG Amplifier Cable	Investigational (US Only)
GENius Jr. Remote Control	Investigational (US Only)
Remote Control Cable 15 or 25ft	Investigational (US Only)
Power Cord, North America	Investigational (US Only)

Power Cord, UK	Market Released (UK Only)
Power Cord, Continental EU	Market Released (Continental EU)

** Sites in Canada will not use PVAC GOLD in the study until Health Canada approval is obtained.



3 DESCRIPTION OF ANALYSIS

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

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

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

3.1 General Summaries

3.1.1 Description of Baseline Variables

Standard baseline and relevant medical history will be collected on the case report forms (CRFs) for all enrolled subjects. Baseline variables to be summarized include, but are not limited to: age, sex, race, physical exam findings, arrhythmia history, arrhythmic symptoms, baseline electrocardiogram (ECG) interpretation, AF medication history, baseline Mini-Mental State Exam (MMSE) score, baseline $CHADS_2$ score and $CHADS_2$-VaSC.

For continuous variables, mean±standard deviation, median, and range will be reported. For categorical variables, frequency and percentage will be reported. Summaries of

baseline information and relevant medical history will be summarized for all enrolled subjects, all subjects with a Phased RF ablation procedure (e.g. at least one Phased RF catheter placed in the left atrium), subjects randomized to the pulmonary vein stenosis (PVS) assessment cohort[redacted].

3.1.2 Summary of Ablation Procedures

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

3.1.3 Special Considerations

3.1.3.1 Missing Data

In general, tipping point analysis methods will be utilized to evaluate the impact of missing data. The analysis details will be specified for individual objectives in the following section.

3.1.3.2 Randomization

Upon confirmation that all inclusion and no exclusion criteria have been met, the Patient Informed Consent form has been signed, and baseline testing has been completed, a subject (except the first enrolled subject at a study center) may be randomized to either [redacted] the PVS assessment cohort, or to the no additional testing cohort. The first enrolled subject at each study center is automatically assigned to the no additional testing cohort.

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

[redacted].

The remaining subjects will be assigned to the no additional testing cohort.

To implement the requirements above, the randomization will be centralized and not stratified by study center. A Medtronic statistician will create the randomization schedule. [redacted]

3.1.3.3 PVAC and PVAC GOLD catheter use

If Phased RF ablation procedures are performed with more than one PVAC model, subgroup analyses may be performed on the primary and secondary objectives as well [redacted] by PVAC model. Specifically, should the need for a subgroup analysis occur, three subgroups will be defined as subjects ablated with only the PVAC catheter (index and reablation procedure), subjects ablated with only the PVAC GOLD catheter (index and reablation procedure), and subjects ablated with both

the PVAC and PVAC GOLD catheter (e.g. index procedure with PVAC catheter and reablation procedure with PVAC GOLD catheter). For each of these objectives, Fisher's Exact test would then be used to assess the heterogeneity of the results by PVAC catheter subgroup should the need for a subgroup analysis arise.

3.1.4 Reports for Which This Statistical Analysis Plan Applies

3.1.4.1 PMA Report

This SAP applies to the PMA report for the VICTORY AF study. The visit cutoff date will be the day on which 300 ablated subjects have completed the 30 day post reablation procedure visit or have had the opportunity for a reablation visit (between 0 and 6 months after the index procedure) meaning the subject has completed the 6-month post-index ablation visit or exited the study prior to a reablation procedure.

Alternatively, the study may stop early for futility prior to completing enrollment if more than 6 procedure and/or device related strokes occur within the 30 day peri-procedural period.

3.1.4.2 Final Report

This SAP applies to the final report for the VICTORY AF study which will take place once all enrolled subjects have had the opportunity to have a 6 month visit following their final procedure, or official study closure defined as when Medtronic and/or regulatory requirements have been satisfied per the Clinical Investigational Plan (CIP), whichever occurs first. There will be no visit cut-off date for the final report. Instead, all the available data at the time of data freeze will be included in the final report.

3.2 Primary Objective: 30-day Procedure and/or Device Related Stroke Rate

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

3.2.1 Hypothesis

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

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

The formal statistical hypothesis for the primary objective is:
H_o: $\pi \geq 3.5\%$
H_a: $\pi < 3.5\%$
where π is the true 30-day post ablation procedure (index or reablation) procedure and/or device related stroke rate.

3.2.2 Definition of Procedure and/or Device Related Stroke

Procedure and/or device related strokes are defined as events classified by the Clinical Events Committee (CEC) meeting all of the requirements in Table 5 in the VICTORY AF CIP (version 5). Specifically, the stroke must have a symptom onset date within 30 days of an ablation procedure where at least one phased RF catheter is deployed into the left atrium (i.e. placed in the left atrium with Phased RF energy delivered) and be considered related to the procedure and/or device by the CEC.

Specifically, in the Medtronic use only CRF (MDT ADVERSE EVENT), the following fields must be checked in relation to the CEC determination:

- Adverse Event is denoted neurological related with a diagnosis of "stroke"
- Adverse Event is denoted as Related to the Phased RF study procedure and/or related to one or more of the following system components: PVAC, PVAC GOLD, MAAC, MASC, or Medtronic GENius™ Multi-Channel RF Generator
- Adverse Event is denoted as "Yes" for meeting the periprocedural definition

Additionally, the following values are required on the relevant procedure CRF (treatment or reablation) to meet the primary endpoint:

- Time of initial Phased RF Catheter deployment in left atrium must be non-missing
- At least one record of Phased RF energy delivery must be present in the PVAC/PVAC GOLD, MAAC, and/or MASC ablation log CRF forms
- Non-investigation catheter use in the left atrium must NOT be checked
- The onset date of the stroke must be no more than 30 days following the index procedure (if stroke occurs prior to any reablation procedure) or no more than 30 days following a reablation procedure if stroke occurs following a reablation procedure.

3.2.3 Experimental Design and Analysis Methods

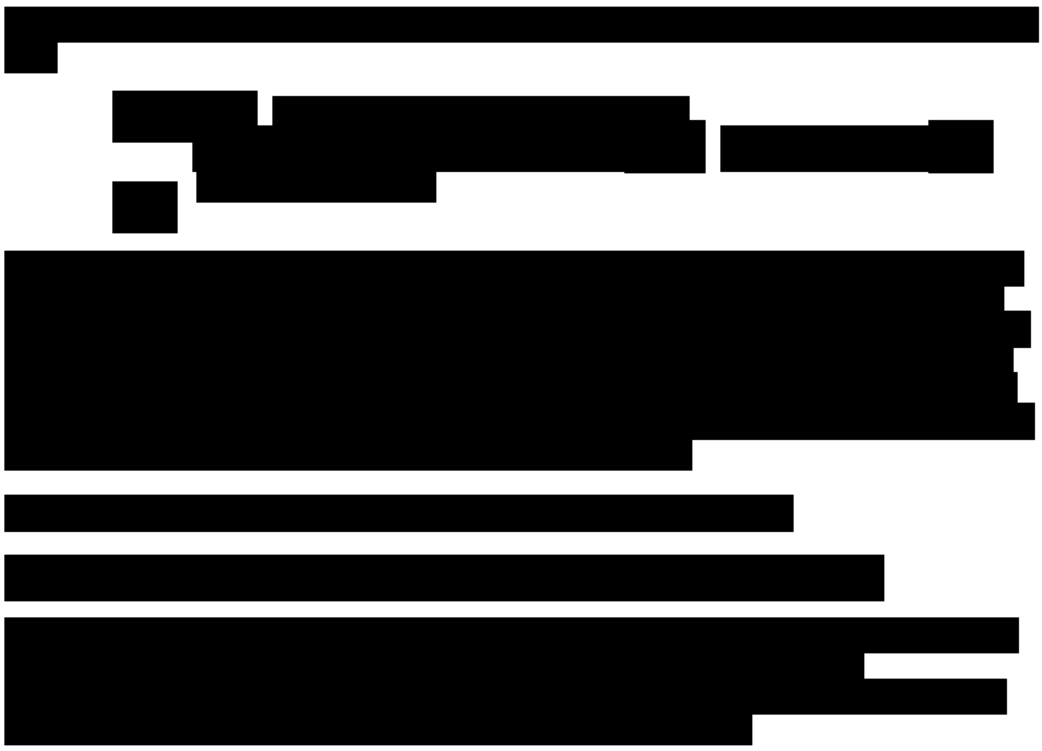
This study is a prospective, unblinded, multi-center, worldwide clinical study designed to evaluate the procedure and/or device related peri-procedural stroke rate within 30 days of an ablation procedure with the Phased RF System. The study will be considered successful if the primary objective is met.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

For computing the peri-procedural stroke rate, the denominator will include:

1. All subjects with at least one ablation procedure attempt where at least one of the Phased RF catheters was deployed into the left atrium with Phased RF energy delivered and have at least 30 days of post-procedural follow-up, AND
2. Subjects with a procedure and/or device related peri-procedural stroke as classified by the CEC within 30-days of a Phased RF procedure regardless of the subject's follow-up duration.

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

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



3.2.4 Sample Size Methods and Assumptions

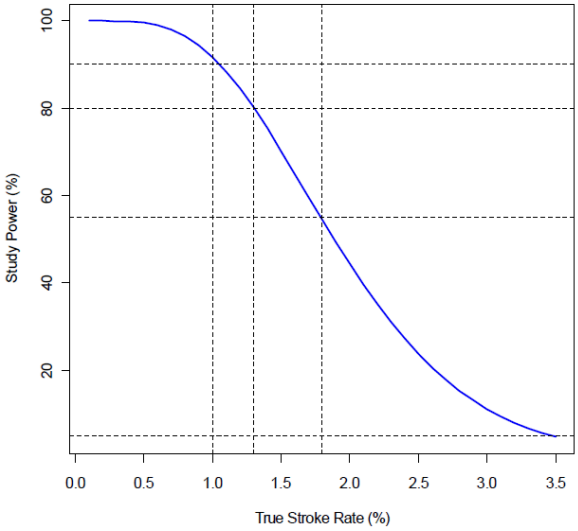
A sample size of 300 subjects completing the 30-day post procedure follow-up visit and having the opportunity for a reablation procedure (i.e. completing the 6- month follow-up visit) or having a reablation procedure and completing the 30-day post-reablation visit provides at least 80% power to test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

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

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

Assuming an annualized attrition rate of 10%, a uniform reablation rate of 30% within 180 days of the index ablation procedure, and a conservative 11% pre-procedure attrition rate up to 350 enrolled subjects will be required to ensure that at least 300 subjects complete the 30-day post ablation follow-up visit and have the opportunity for a reablation procedure or have a reablation procedure and complete the 30-day post-reablation procedure visit.

Figure 1: Study Power versus True Stroke Rate



Note: Power curve computed using exact binomial method.

3.2.5 Determination of Subjects for Analysis

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

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

3.2.6 Missing Data

The impact of missing data on the analysis of this objective is expected to be small since only a 30 day post-ablation follow-up period is required. However, missing data could arise if a subject undergoes a Phased RF ablation procedure, does not have procedure and/or device related peri-procedural stroke, and exits the study prior to their 30 day post-procedure visit. These subjects will not be included in the primary analysis cohort, but a tipping point analysis will be employed to determine the impact of the missing data on the observed stroke rate should the issue of missing data arise.

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

study across a range of reablation rates and reablation stroke rates. Sample R code for performing the modified tipping point analysis can be found in the Appendix.

3.2.7 Pre-specified Subgroup Analyses

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

Additionally, if more than one PVAC catheter model (PVAC or PVAC GOLD) is used during the VICTORY AF study a subgroup analysis will be performed to assess the peri-procedural stroke rate by PVAC catheter subgroup as described in section 3.1.3.3.

3.3 Secondary Objectives

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

Confirm the 6-month post-procedural effectiveness.

3.3.1.1 Hypothesis

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

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

3.3.1.2 Definition of 6 Month Effectiveness

6-Month effectiveness will be defined as:

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

3.3.1.3 Analysis Methods

Acute effectiveness for each subject will be determined as described in section 3.3.2.2. In order for a subject to meet the acute procedural success criterion for the 6-month effectiveness endpoint, the subject must be an acute procedural success for their index and reablation procedure (if required). Holter recordings will be completed at the baseline and 6-month post final Phased RF ablation procedure. Holter recordings will be read and summarized by the Holter core laboratory. For the baseline and 6-month post-ablation procedure Holter recording, the percentage of time in clinically significant AF (AF > 10 minutes) will be calculated as the total number of seconds in clinically significant AF divided by the total Holter recording time in seconds. The percent reduction from baseline will be calculated as the difference of the percentage of time in clinically significant AF between the baseline and 6-month post-ablation procedure visit divided by the percentage of clinically significant AF at baseline. Subjects with at least a 90% reduction in clinically significant AF will be considered successful for the Holter component of 6-month effectiveness endpoint. Adjustments to all cardiovascular medications including antiarrhythmic drugs and dates of all DC cardioversions will be captured on the case report forms.

Only those subjects that have a baseline and 6-month post-procedure 48-hour Holter data that are readable by the core lab or are missing Holter data but were 6-month effectiveness failures based on other criteria at the time of the visit cutoff date will be included in the analysis of this objective. Specifically, the denominator for the 6-month effectiveness rate will include all subjects that had at least one Phased RF ablation procedure where an investigational catheter was deployed into the left atrium (i.e. placed in the left atrium and phased RF energy delivered) and have baseline and 6-month Holter data available or do not have Holter data available but were 6-month effectiveness failures based on other criteria. The numerator will include all subjects in the denominator that meet all four 6-month effectiveness conditions. A two-sided 95% exact confidence interval for 6-month effectiveness rate will be calculated.

[redacted]

[redacted]

3.3.1.4 Determination of Subjects for Analysis

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

3.3.1.5 Confidence Interval Width

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

Based on the following assumptions:

- Up to 350 subjects will be enrolled
- 300 subjects are required to complete the 30-day post-ablation visit and have the opportunity for a reablation procedure (i.e. complete 6-month visit) or complete the 30-day post-reablation visit if a reablation procedure is required
- Total of 40 study centers
- 9 months to activate the 40 centers
- Enrollment rate of 0.4 subjects per center per month once activated
- 30% of subjects will be re-ablated prior to their 6-month visit
- 10% annualized attrition rate

It was estimated via a simulation study that approximately 275 subjects would complete the 6-month Holter assessment. Assuming 200 subjects have evaluable baseline and 6-month Holter data and the observed 6-month effectiveness rate is 55%, then the exact 95% two-sided confidence interval should have a width no larger than 14.2% with a lower limit of at least 47.8%. Similarly, if the observed 6- month effectiveness rate is 50%, the confidence interval width should be no greater than 14.3% with a lower limit of at least 42.9%.

3.3.1.6 *Missing Data*

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

3.3.1.7 *Pre-specified Subgroup Analysis*

If more than one PVAC catheter model (PVAC or PVAC GOLD) is used during the VICTORY AF study a subgroup analysis will be performed to assess the 6-month post-procedural effectiveness by PVAC catheter subgroup as described in section 3.1.3.3.

3.3.2 Secondary Objective #2: Acute Procedural Success

Confirm acute post-procedural effectiveness.

3.3.2.1 *Hypothesis*

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

3.3.2.2 *Definition Acute Procedural Success*

For the index Phased RF ablation procedure, acute procedural success is defined as meeting all four of the following conditions:

1. Only Phased RF catheters used in the left atrium to achieve procedure success AND
2. All accessible pulmonary veins were isolated (entrance block)
3. Complex fractionated atrial electrograms (CFAEs) and high frequency intracardiac electrogram amplitudes were mapped and ablated as necessary with Phased RF System
4. Sinus rhythm is restored at the end of the ablation procedure (with or without cardioversion)

For a reablation Phased RF procedure, acute procedural success is defined as meeting at least conditions (1) and (4) of the acute procedural success definition above.

3.3.2.3 *Analysis Methods*

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

attempt since the source of recurrent AF will be unknown. SAS code similar to the PROC FREQ statements in section 3.3.1.3 will be used to compute the two-sided 95% exact confidence interval for the acute success rate.

In addition to calculating the acute success rate on a per subject basis, the acute success rate will be calculated on a per procedure basis. The denominator for the per procedure rate will be all Phased RF procedures where at least one Phased RF catheter was deployed into the left atrium and Phased RF energy delivered. The numerator will be all Phased RF procedures in the denominator that meet the acute success definition. A two-sided 95% confidence interval for this rate will also be calculated using the method of Rao and Scott for clustered binary data since subjects may have up to two ablation procedures. A SAS macro to calculate the Rao and Scott confidence interval can be found in the directory:
V:\AF Solutions\VICTORYAF\Documents\Statistical_Analysis_Plan.

3.3.2.4 Determination of Subjects for Analysis

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

3.3.2.5 Missing Data

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

3.3.2.6 Pre-specified Subgroup Analysis

If more than one PVAC catheter model (PVAC or PVAC GOLD) is used during the VICTORY AF study a subgroup analysis will be performed to assess the 6-month post-procedural effectiveness by PVAC catheter subgroup as described in section 3.1.3.3.

3.3.3 Secondary Objective #3: Pulmonary Vein Stenosis

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

3.3.3.1 Hypothesis

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

3.3.3.2 Definition of Pulmonary Vein Stenosis

Pulmonary vein stenosis is defined as a greater than 70% reduction in the baseline luminal diameter occurring in any one or more of the pulmonary veins[1].

Specifically, a subject with an ablation attempt where at least one Phased RF catheter was deployed in the left atrium (i.e. placed in left atrium with Phased RF energy delivered) will be considered PVS positive if they have a greater than 70% reduction from baseline in either the major axis diameter or the minor axis diameter in any of the six pulmonary veins (right superior, right inferior, right middle, left superior, left inferior, or left common).

[1] Calkins H, Kuck KH, Cappato R, et al. 2012 HRS/EHRA/ECAS Expert Consensus on Catheter and Surgical Ablation of Atrial Fibrillation. Heart Rhythm. 9(4): 632-696.

3.3.3.3 Analysis Methods

One hundred (100) subjects will be randomized to the PVS assessment cohort. Subjects randomized to the PVS assessment cohort will have a CT-scan or MRI scan at their baseline visit and a CT-scan or MRI scan for PVS assessment at their first 3-month post-ablation visit (e.g. subjects with a reablation procedure following their 3-month post index ablation assessment will not have another scan at their 3-month post reablation visit). The CT/MRI core laboratory will record the major and minor axis diameter in mm of each pulmonary vein at the baseline and 3-month post-ablation visit. For each pulmonary vein and axis, the change in pulmonary vein diameter will be calculated as: ((3-month post-ablation diameter minus baseline diameter)/baseline diameter) $\times$100%. If this value is less than or equal to negative 70% for either the major or minor axis on any of the six pulmonary veins, the subject will be considered PVS positive. For computing the PVS rate at 3 months post ablation, the denominator will be all subjects that are randomized to the PVS assessment cohort, have at least one ablation procedure with one or more Phased RF catheters deployed in the left atrium with Phased RF energy delivered, and either have evaluable CT or MRI scans available at their baseline and 3-month follow up visits for at least four of the six pulmonary veins or meet the definition of PVS positive on at least one axis of one of the six pulmonary veins. The numerator will be all subjects included in the denominator that meet the definition of PVS on at least one axis of one of the six pulmonary veins. A two-sided 95% exact confidence interval for the 3-month post-procedure PVS rate will be calculated. SAS code similar to the PROC FREQ statements in section 3.3.1.3 will be used to compute the two-sided 95% exact confidence interval for the PVS rate.

Additionally, descriptive statistics and/or graphical methods will be used to summarize the major and minor diameter at baseline and 3-months post-ablation as well as percent change in diameter for each pulmonary vein.

3.3.3.4 Determination of Subjects for Analysis

Only those subjects that are randomized to the PVS assessment cohort, have at least one ablation procedure with one or more Phased RF catheters deployed in the left atrium with Phased RF energy delivered, and have CT or MRI scans at baseline and at the 3-month follow-up visit (or 3-month post-reablation visit if subject was reablated and reablation occurred prior to the 3-month post index ablation visit) that are readable by the core lab for at least four of the six pulmonary veins or have a greater than 70% reduction in vein diameter in one or more veins will be included in the analysis of this objective.

3.3.3.5 Confidence Interval Width

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

3.3.3.6 Missing data

Subjects missing a readable baseline or 3-month follow-up MRI or CT-scan in more than two pulmonary veins will not be included in the main analysis cohort for this objective unless they are PVS positive in one of their observed pulmonary veins. However, should the issue of missing data arise; all subjects randomized to the PVS assessment cohort

with at least one Phased RF catheter deployed in the left atrium (i.e. placed in the left atrium with Phased RF energy delivered) will be included in a tipping point analysis regardless of whether MRI or CT-scans are available. Specifically, subjects randomized to this cohort, but missing an evaluable baseline or 3-month MRI or CT-scan in more than two pulmonary veins will be included as PVS negative and iteratively added as PVS positive in the tipping point analysis.

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