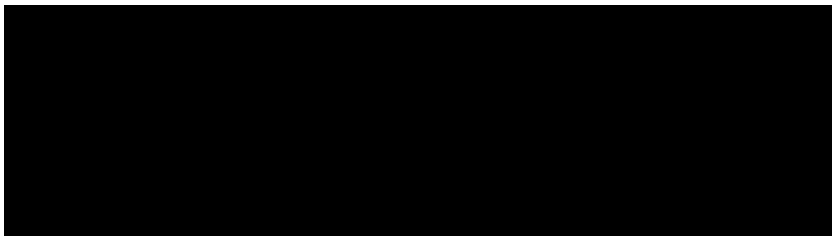
Statistical Analysis Plan

Evaluation of the VISITAG SURPOINT™ Module with External Processing Unit (EPU) when used with the THERMOCOOL SMARTTOUCH® SF and the THERMOCOOL SMARTTOUCH® Catheters for Pulmonary Vein Isolation (PVI) (SURPOINT COA)

Protocol# BWI_2017_06

Version 3.0

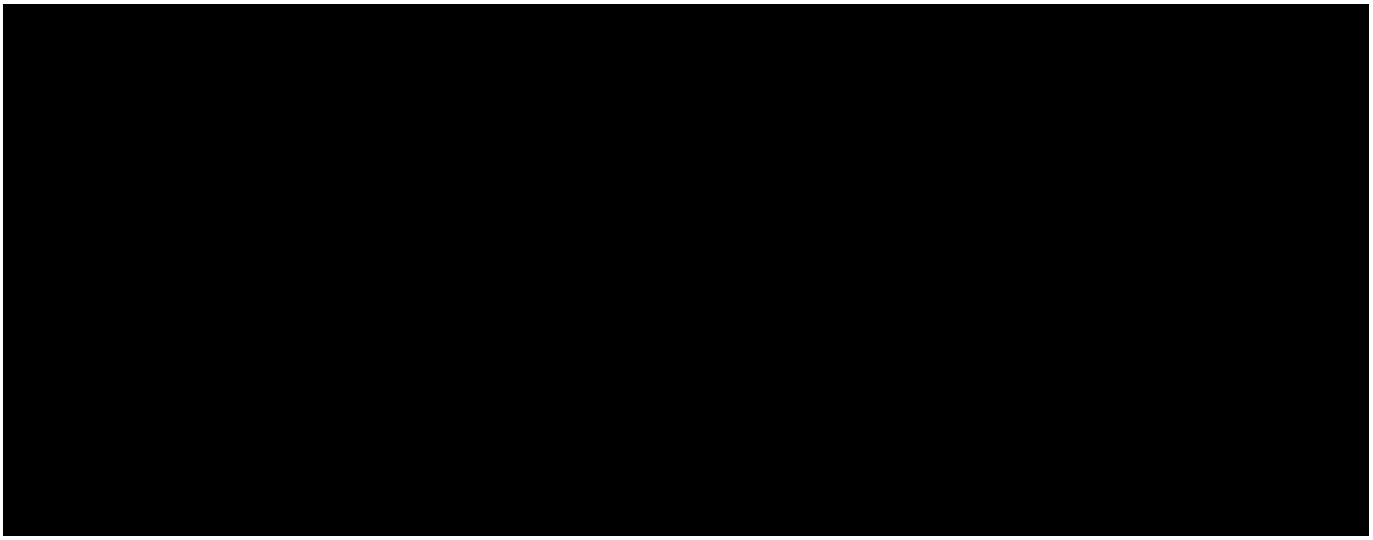


Evaluation of the VISITAG SURPOINT™ Module with External Processing Unit (EPU) when used with the THERMOCOOL SMARTTOUCH® SF catheter for Pulmonary Vein Isolation (PVI)

(SURPOINT COA)

SAP Version: 3.0

The following individuals have reviewed this version of the Statistical Analysis Plan and are in agreement with the content:



[redacted]

SAP Version	Revision Date (DD/MM/YYYY)	List of Changes
3.0	January 21, 2020	• Section 3, 8, 9.4, 9.4.1, 9.4.3, 9.4.6, 9.5: typos • Section 9.4.1: changed "predictive posterior probability" to "posterior probability" • Section 9.4.6: changed "Interaction terms will be examined" to "Interaction terms may be examined"
2.0	May 24, 2018	• Study Name: added "and the THERMOCOOL SMARTTOUCH®" to the study name • Section 1, 2, 8: added 50 subjects using ST catheter with EPU as the study subjects and changed the number of study sites to be 45 . • Section 5.1.2: added "…, except atrio-esophageal fistula and PV stenosis [49,50], which may also be considered as primary adverse events if occurring

		greater than 7 days post the ablation procedure" to the primary safety endpoint definition • Section 5.2.2: added 12-Month PAE Rate as secondary endpoint • Section 9.4 Analyses of Primary Endpints: added anlaysis population for the primary effectiveness and safety endpoint in section 9.4. • Section 9.4.1Final Analysis: added "Note that the final analysis will be performed if early success is not declared at either of the two interim looks. If early success is declared at either of the two interim looks, a summary of the primary endpoints based on full 12-month follow-up will be provided." • Section 9.4.2 Interim Analyses: o Added "For the safety endpoint, among patients with full 12-month follow-up at the time of the interim analyses, any atrio-esophageal fistula and PV stenosis occurring post procedure will be deemed PAE." o Specified the timing of interim analysis as "once subjects who are treated using STSF catheter with EPU who have completed 3-month (6-month) follow-up" and the interim analysis will be based on the data collected among subjects who are treated with STSF catheter only. • Section 9.4.5 Subgroup Analyses: o Added 95% confidence interval and Fisher's Exact o Added Fisher-Freeman-Halton Exact Test when number of subgroup is greater than 2 o Removed gender and site from the subgroup analysis o Changed the cut points of operator's ablation procedure experience level to 75

		left atrial ablation procedures for atrial fibrillation in the past 12 months ○ Changed the cut point of contact force to be <=10, 11-15, 16-20 and >20 grams • Section 9.4.5.1 Poolability by Gender Analysis: sdded sex-specific 90% confidence intervals of the primary endpoints • Removed the term “Evaluable Subjects” from the SAP

TABLE OF CONTENTS

List of Abbreviations

AAD	antiarrhythmic drug
AF	atrial fibrillation
AFL	atrial flutter
AT	atrial tachycardia
EPU	external processing unit
ISTH	International Society on Thrombosis and Haemostasis
PAE	primary adverse event
PP	per-protocol
PV	pulmonary vein
PVI	pulmonary vein isolation
QOL	quality of life
RF	radiofrequency
SAE	serious adverse event
SF-12	12-Item Short Form Survey
SP	Safety Population
ST	THERMOCOOL SMARTTOUCH® catheter
STSF	THERMOCOOL SMARTTOUCH® SF catheter
UADE	unanticipated adverse device effect

1. STUDY DESIGN

The SURPOINT COA study is a prospective, multicenter, non-randomized clinical evaluation of the VISITAG SURPOINT Module with EPU when used with the THERMOCOOL SMARTTOUCH® SF catheter (STSF) catheters or the THERMOCOOL SMARTTOUCH® (ST) catheter in treating subjects with symptomatic paroxysmal atrial fibrillation (PAF) who have failed at least one antiarrhythmia drug. A maximum of 330 subjects will be enrolled across up to 45 sites. Two hundred eighty (280) subjects will be treated using the STSF catheter with EPU and 50 subjects will be treated using the ST catheter with EPU. A few sites will be selected to enroll subjects to be treated only with the ST catheter. The remaining sites will enroll subjects to be treated with the STSF catheter. Two interim analyses are planned to take place after all subjects who are treated using the STSF catheter with EPU have completed their 3-month and 6-month follow-up visits for the evaluation of early success. The planned interim analysis will be based on data collected only in the subjects who are treated using STSF catheter with EPU. The final analysis of the primary effectiveness and safety endpoints will be based on all subjects's full 12-month follow-up data. Effectiveness and safety endpoints defined in association with the primary study objectives will be compared to the predetermined performance goals.

Enrolled subjects who satisfy all eligibility criteria will undergo the ablation procedure with the catheters and VISITAG SURPOINT Module. After the study ablation procedure, subjects will enter a 3-Month blanking period (Day 0-90). After the blanking period, subjects will enter the evaluation period (Days 91-365). Subjects having AF recurrence and/or receiving therapeutic interventions during the evaluation period will be considered effectiveness failures.

All subjects will undergo follow up visits at defined intervals (refer to Table 5-1 Schedule of Treatments and Evaluations in protocol). Subjects complete the SURPOINT COA study after the 12-month follow up visit.

2. TREATMENT ASSIGNMENT

This is a single-arm study. The only treatment assigned is the THERMOCOOL SMARTTOUCH® SF (STSF) catheter and the THERMOCOOL SMARTTOUCH® (ST) catheter using VISITAG SURPOINT™ Module with External Processing Unit (EPU).

3. RANDOMIZATION AND BLINDING PROCEDURES

This study is a non-randomized single-arm study. An independent group will perform the Bayesian interim analyses. The sponsor is not blinded to individual or aggregated data.

4. INTERVAL WINDOWS

The required schedule for subject treatments and evaluations is summarized in Table 5-1 of the study protocol.

5. PRIMARY AND SECONDARY ENDPOINT(S) AND ASSOCIATED HYPOTHESES

5.1 Primary Endpoints and Associated Hypotheses

5.1.1 Primary Effectiveness Endpoint

The primary effectiveness endpoint of this study is the effectiveness success rate at Month 12, defined as the proportion of subjects who are freedom from documented (symptomatic and asymptomatic) atrial fibrillation, atrial flutter and atrial tachycardia (AF/AFL/AT) (hereinafter collectively referred to as “atrial tachyarrhythmias") recurrence (episodes ≥ 30 secs on TTM or continuously recorded on the standard 12-leads ECG or holter) during the evaluation period (Day 91-365) and freedom from the following failure modes:

- Acute procedural failure, including:
  - Failure to confirm entrance block in all pulmonary veins at the end of procedure
- Repeat ablation failure, including:
  - > 1 repeat ablation procedures during the 3-Month Blanking Period (Day 0-90) after the index ablation procedure.
  - Any repeat ablation procedure during the evaluation period.
- DC cardioversion for AF/AFL/AT following the 3-month blanking period
- Surgical treatment for AF/AFL/AT after the index ablation procedure.
- AAD failure: Taking a new AAD for AF, a previously failed AAD at a greater than the highest ineffective historical dose during the evaluation period.

This study is designed to compare the primary effectiveness of the VISITAG SURPOINT Module with EPU to a pre-determined performance goal of 50%, which is indicated as the minimum acceptable success rate at 12 months for a paroxysmal AF population in the 2017 HRS/EHRA/ECAS/APHRS/SOLAECE consensus statement.

The final analyses for primary effectiveness endpoint will apply Bayesian methods and use a beta-binomial model [1].

The hypotheses to be tested for this evaluation are:

$$H_0: p \leq 0.50 \qquad \text{vs.} \qquad H_A: p > 0.50,$$

where p is the effectiveness success rate

5.1.2 Primary Safety Endpoint

The primary safety endpoint is the proportion of subjects with any primary adverse event (PAE) occurring within 7 days following an AF ablation procedure (including the initial and repeat procedures) using the STSF/ST catheter with EPU, except atrio-esophageal fistula and PV stenosis [6,7], which may also be considered as primary adverse events if occurring greater than 7 days post the ablation procedure. The PAE rate will be compared against the performance goal of 14%.

The final analyses for primary safety endpoint will apply Bayesian methods and use a beta-binomial model [1].

The hypotheses to be tested for this evaluation are:

$$H_0: q \geq 0.14 \qquad \text{vs.} \qquad H_A: q < 0.14$$

where q is the PAE rate.

5.2 Secondary Endpoints

No formal statistical hypothesis and inferential statistics will be formulated and performed for the secondary endpoints.

5.2.1 Secondary Effectiveness Endpoints

- Acute Procedural Success
  - % of subjects with ipsilateral PVI (entrance block) at the end of the procedure
  - % of subjects with ipsilateral PVI (entrance block) after first encirclement (evaluated prior to the 30-minute waiting period and adenosine challenge)
  - % of touch-up (ablation of acute reconnection) among all targeted veins
  - Anatomical location of acute PV reconnection after first encirclement
- Repeat ablation procedures during 12-month period post-procedure
  - Incidence (%) of repeat ablation procedures
  - % PVs re-isolated among all of the targeted PVs at repeat procedure

- % repeat ablation procedures requiring new linear lesions and/or identifying new foci outside of initially isolated area among the repeat ablation procedures

- 12-Month Single Procedure Success
  - The 12-month single procedure success is defined as freedom from documented AF/AFL/AT recurrence (episodes $\geq$ 30 secs) during the Evaluation Period after a single ablation procedure and off AADs. Any repeat ablation procedure or AAD therapy will be deemed effectiveness failure for this analysis.

5.2.2 Secondary Safety Endpoints

- 12-Month PAE Rate:

  12-Month PAE Rate is the cumulative incidence of primary adverse events occurring within seven (7) days following an AF ablation procedure using study catheters with EPU and any late onset atrio-esophageal fistula or PV stenosis through 12 months

- Incidence of Unanticipated Adverse Device Effects (UADEs)

- Incidence of Serious Adverse Events (SAEs) within 7 days (early onset), >7 to 30 days (peri-procedural) and >30 days (late onset) of initial ablation

- Incidence of bleeding complication (ISTH definitions): a) major bleeding, b) clinically relevant non-major and c) minor bleeding

5.3 Additional Endpoints

No formal statistical hypothesis and inferential statistics will be formulated and performed for the additional endpoints.

- Procedural Data:
  - Total procedure time, PVI time, RF application time, mapping time and RF application time per lesion
  - Total Fluoroscopy Time
  - Fluid delivered from the study catheter
  - Location of RF applications, number of RF applications
  - RF Ablation parameters per application (e.g. temp, power, impedance, CF etc.)
  - Device(s) utilized (per ablation)
  - VISITAG™ Settings

- CF range
- Power range
- Tag Index Assessment per anatomical region

- Quality of Life (QOL): SF-12

5.4 Health Economic Data

The primary health economic data will include the cost and frequency of hospitalization for the study index ablation procedure, as well as any additional hospitalizations during the study period. The health care utilization during hospitalizations will be assessed by utilizing all data available for this study such as copies of the subject's hospital bills (UB04) and/or itemized hospital bills.

The health economic data associated with follow up care will include any repeat ablation procedure for treating arrhythmia, any inpatient or outpatient visit (including ER admissions) to address post-procedural complications or any procedure related condition and any inpatient or outpatient visit (including ER admissions) related to arrhythmia and cardiovascular conditions.

6. LEVEL OF SIGNIFICANCE

The type I error for the interim and final analyses of the primary endpoints is controlled at one-sided 5%.

7. ANALYSIS SETS

For the analysis of study endpoints, the analysis populations defined in the following will be used:

- Safety Population: The SP will consist of all enrolled subjects who have undergone insertion of the STSF/ST catheter and use of the VISITAG SURPOINT™ Module with EPU. The safety population (SP) will be used to analyze safety endpoints.

- Per Protocol (PP) Population: The PP population will include subjects who satisfy the following criteria. The PP population will be used for the analysis of effectiveness endpoints.
  - are enrolled and meet all eligibility criteria
  - have undergone RF ablation
  - are treated with the STSF/ST catheters with the VISITAG SURPOINT™ Module with EPU, and have been treated for the study-related arrhythmia

- Full Set Effectiveness Population: This population will include those who have met the following criteria. The full set effectiveness population will be used to analyze the effectiveness endpoints.
  - are enrolled
  - have undergone RF ablation
  - are treated with the STSF/ST catheters with the VISITAG SURPOINT™ Module with EPU, and have been treated for the study-related arrhythmia

8. SAMPLE SIZE JUSTIFICATION

The final analyses for primary safety and effectiveness endpoints will apply Bayesian methods and use a beta-binomial model [1].

The power calculations for the Bayesian adaptive design are presented in the simulation report Appendix B Table 6 (probability of success). Under the assumption of 65% success rate for primary effectiveness and 8% rate for primay safety, with 330 subjects, assuming 10-15% attrition rate, we will have more than 90% power for declaring success for each of the primary endpoints controlling the type-I error at 5%.

The total of 330 enrolled subjects includes 280 subjects who will be treated using STSF catheter with EPU and 50 subjects be treated using ST catheter with EPU. Approximately 30 subjects may be excluded or discontinued before receiving treatment assuming 10-15% attrition rate.

9. STATISTICAL ANALYSIS METHODS

9.1 General Conventions

In general, descriptive statistics will summarize all primary, secondary, and additional endpoints as appropriate. For continuous variables, number of subjects/events, mean, standard deviation, median, 25% percentile, 75% percentile, minimum, and maximum will be provided. For categorical variables, frequency and percentage will be presented for each category.

9.2 Subject Disposition

Disposition of the study subjects are defined as the following.

- **Enrolled Subjects**: subjects who sign the informed consent.
- **Excluded Subjects:** subjects who do not have the STSF/ST catheter inserted or have the STSF/ST catheter inserted but do not undergo ablation with VISITAG SURPOINT™ Module. Subjects who have the STSF/ST catheter inserted but do not

undergo ablation with VISITAG SURPOINT™ Module will be followed for 12 months.

- **Lost to Follow-up Subjects:** subjects who are enrolled and have STSF/ST catheter inserted and undergo ablation with VISITAG SURPOINT™ Module, but contact is lost after most recent follow-up visit (despite 3 documented attempts).
- **Withdrawn / Early Termination Subjects:** subjects who withdraw consent for study participation or are withdrawn by the investigator or are terminated from the study prior to completion of all follow-up visits.
- **Completed Subjects:** enrolled subjects who completed the 12-month follow-up visit.

9.3 Demographics and Baseline Characteristics

Subject demographics, medical history, AAD medical history and other baseline data will be summarized descriptively for all enrolled subjects as well as the safety and PP populations.

9.4 Analysis of Primary Endpoints

The primary effictiveness endpoint is the proportion of patients that are free from primary effectiveness failure at Month 12. The failure modes are defined in the section 5.1.1. The effectiveness success rate at Month 12 will be compared against the performance goal of 50%. The final analyses will apply the Bayesian methods using a beta-binomial model. The analysis population for the primary effectiveness endpoint will be the per protocol (PP) population.

The primary safety endpoint is the proportion of patients that had Primary Adverse Event (PAE) within 7 days (PV stenosis and atrio-esophageal fistula may occur up to 3 months). The PAE rate will be compared against the performance goal of 14%. The final analyses will apply the Bayesian methods using a beta-binomial model. The analysis population for the primary safety endpoint will be the safety population.

9.4.1 Final Analysis

The primary goal of the trial is to demonstrate effectiveness and safety. For the trial to be successful, both endpoints must be statistically significant relative to their respective PG goals.

The effectiveness endpoint will be assessed by testing the hypotheses:

$$H_0: \Pr(p > 0.5|x,n) \leq 0.97 \quad \text{vs.} \quad H_A: \Pr(p > 0.5|x,n) > 0.97$$

where p is the responder rate, x is the observed number of patients that are failure-free through 12 months ("responders"), and n is the number of subjects in the PP population. If the posterior probability of the primary effectiveness endpoint meeting the 50% PG is greater than 97%, then we meet the threshold for primary effectiveness success.

We model the number of responders

$$X \sim \text{Binomial}(n, p),$$

We use a Beta (0.01, 0.01) prior distribution. This prior is centered at 50% and has an effective sample size of 0.02 observations.

Then the posterior distribution is

$$(p|x, n) \sim \text{Beta}(0.01 + x, 0.01 + n - x).$$

Subjects with missing data on the effectiveness endpoint will have their outcomes multiply imputed from a longitudinal model.

Similarly, the hypothesis test for the safety endpoint is:

$$H_0: \Pr(q < 0.14|y, n) \leq 0.95 \qquad \text{vs.} \qquad H_A: \Pr(q < 0.14|y, n) > 0.95$$

where q is the PAE rate, y is the observed number of subjects who had PAE and n is the number of subjects in the safety population. If the posterior probability of the primary safety endpoint meeting the 14% PG is greater than 95%, then we meet the threshold for primary safety success.

We model the number of patients with PAE as

$$Y \sim \text{Binomial}(n, q)$$

with Beta(1, 1) prior distribution on q. No imputation for missing data will be performed for the safety endpoint.

The trial will be considered a success if BOTH

1. $\Pr(p > 0.5|x, n) > 0.97$ AND
2. $\Pr(q < 0.14|y, n) > 0.95$.

These thresholds control the overall Type I error rate for the trial below one-sided 5%. The Type I error for each endpoint individually is also below 5%. The protocol Appendix B contains a detailed description of the statistical methods planned for testing the hypotheses around the primary effectiveness and safety endpoints.

Note that the final analysis will be performed if early success is not declared at either of the two interim looks. If early success is declared at either of the two interim looks, a summary of the primary endpoints based on full 12-month follow-up will be provided. In addition, both safety

and effectiveness results will be descriptively summarized separately for patients treated with the ST and STSF catheters.

9.4.2 Interim Analysis

Two interim analyses are planned. The first will occur once all subjects who are treated using STSF catheter with EPU have completed their 3 months follow-up. The second interim will occur when all subjects who are treated using STSF catheter with EPU have completed their 6 months follow-up. The planned interim analysis will be based on data collected only in subjects who are treated using STSF catheter with EPU. For the safety endpoint, among patients with more than 3 months of follow-up at the time of the interim analyses, any atrio-esophageal fistula and PV stenosis occurring post procedure will be deemed PAE.

At each interim analysis, the trial will declare early success if the predictive probability of success at the final analysis is greater than or equal to 99%. Early success will be declared at an interim if:

1. The safety objective has been met, and
2. The effectiveness endpoint has greater than or equal to 99% predictive probability of success.

The predictive probability is the probability of observing the success rate larger than 0.50 if the study continues to the end, given the observed data.

All of the subjects will be followed up to 12 months even after we claim success at interim look and submit the results in support of a premarket application. A final CSR will be submitted after all of the subjects complete their 12 months follow-up.

9.4.3 Handling of Missing Data

At the time of each interim analysis, some subjects will not have completed the full 12-month evaluation period. For example, recently enrolled subjects who are currently failure-free but have only been observed for a portion of the observation period will have "censored" final outcomes. Some subjects may still be within the 13-week blanking period, and have no follow-up time during the observation period. Some subjects may be lost to follow-upA longitudinal model will be employed to enable final observations to be multiply imputed for those subjects with partial or no follow up. Details are included in Appendix B of the protocol version 3.0.

The model is a piecewise exponential model for the time-to-failure during the 39-week post-blanking period. The model has three distinct segments: (0, 2], (2, 8], and (8, 39] weeks. The probability of failure during each interval is exponentially distributed, with different hazard rates in each segment. The model is:

$$f(t) = \exp(-th(t)),$$

where

$$h(t) = \begin{cases} \lambda_1 & 0 < t \leq 2; \\ \lambda_2 & 2 < t \leq 8; \\ \lambda_3 & 8 < t \leq 39. \end{cases}$$

These intervals are based on the model used in the ThermoCool Pivotal trial [2].

Noninformative Gamma (1, 1) prior distributions will be used for each λ in the model.

9.4.4 Sensitivity Analyses

To investigate the robustness of primary analysis result of primary endpoints, several sensitivity analyses will be performed. These sensitivity analyses will be performed after all of the subjects complete or reach the 12 months visit and results will be presented in the final CSR.

9.4.4.1 Snap-Shot Binomial Analysis of Primary Endpoints

In the PP population, exact binomial analysis will be performed to assess the primary effectiveness outcome. In the safety population, exact binomial analysis will be performed to assess the primary safety outcome. The subjects with missing outcomes will be excluded from the analysis.

9.4.4.2 KM Curve Analysis

Kaplan-Meier estimate will be used to characterize the time to first AF/AT/AFL recurrence following initial ablation procedures in the PP population. The survival probabilities of AF/AT/AFL recurrence at each of the monthly follow-up time point post blanking along with the corresponding 90% confidence intervals using Greenwood's formula will also be presented. This analysis would be descriptive.

9.4.4.3 Full Set Effectiveness Population

Some subjects in the clinical studies may be enrolled and treated with the study cathether using EPU, however, may be later found not to meet the inclusion and exclusion criteria due to missing documentation or other reasons. In order to assess the effectiveness outcomes of these subjects as well, the exact binomial analysis and the KM analysis will be repeated in the Full Set Effectiveness Population.

9.4.4.4 Alternative Exponential Model for Imputation

In the final Bayesian analysis, a more flexible piecewise exponential model with one segment for each month will also be applied to impute the missing outcomes for the primary effectiveness endpoint.

9.4.4.5 Multiple Imputations of Missing Data in PP Population

Multiple imputation [3] will be used to impute missing data for the effectiveness outcome in the PP population. 5 imputed datasets will be generated (M=5). The MI procedure in sas studio (PROC MI and PROC MIANALYZE) will be used to perform these analyses.

9.4.4.6 Tipping Point Analysis of Missing Data

Tipping point analysis [4] will be performed in the PP population to assess the impact of missing effectiveness outcomes. Tipping point analysis will also be performed in the safety population to assess the impact of missing safety outcomes if there is any.

9.4.5 Subgroup Analyses

For the primary endpoints, subgroup analysis will be performed for the following subgroups after the 12 months follow-up is complete.

PP population will be used for primary effectiveness endpoint and safety population will be used for primary safety endpoint. The number and percentage of subjects with the primary effectiveness and safety endpoints will be presented in each subgroup. Exact 95% confidence intervals will be constructed around the percentages in each subgroup. Fisher's exact test will be used to test for statistical difference between the subgroups at the 5% significance level. Fisher-Freeman-Halton Exact Test will be used when the number of subgroup is greater than two. Since subgroup analyses are unadjusted, any differences especially in subgroups defined based on post-baseline characteristics, may be confounded by differences in baseline characteristics. For e.g., repeat procedure vs. no repeat procedure during the blanking period – patients with more advanced disease at baseline may require a repeat procedure impacting the observed safety and effectiveness rates.

- Age group: <60 vs. >=60 years
- Previously failed AAD Class I&III vs Class II&IV
- Repeat procedure during blanking period: Repeat procedure conducted vs. Not conducted
- Operator's ablation procedure experience level: More experienced (≥ 75 left atrial ablation procedures for atrial fibrillation in the past 12 months) vs. Less experienced (< 75 left atrial ablation procedures for atrial fibrillation in the past 12 months)
- Segments of Tag Index values: above or below or at target

- Contact Force: <=10, 11-15, 16-20 and >20 grams
- Ablation targets

9.4.5.1 Poolability by Gender Analysis

- Deomographics data will be summarized by gender

- Q statistic will be used to compare the primary effectiveness and safety endpoints by gender. A p-value of < 0.15 will be considered statistically significant for an assessment of poolability by gender. The poolability analyses will be conducted in the PP population for primary effectiveness endpoint and will be conducted in the safety population for primary safety endpoint.If the test result is significant, the 90% exact confidence intervals will be constructed around the percentages of primary endpoints by gender.

9.4.5.2 Poolability by Study Sites

To assess the site effect on primary endpoints visually, the success rate at each site will be ploted against the number of subjects from the sites in the PP population. The PAE rate at each site will also be ploted against the number of subjects from the site in the safety population. Any site that appears outlying from general pattern of the rest of sites will be investigated.

- Sites with less than five enrolled subjects will be combined together within their corresponding geographic region in the subgroup analysis so that the combined center(s) will have five or more enrolled subjects. The geographic regions of the U.S. are defined for this analysis as follows: Northeast, Southeast, Great Lakes, Central, and West.

- Q statistic will be used to examine the poolability across sites for the primary effectiveness and safety endpoints. A p-value of <0.15 will be considered statistically significant for an assessment of poolability across the treatment sites. The poolability analyses will be conducted in the PP population for primary effectiveness endpoint and will be conducted in the safety population for primary safety endpoint.

  If the sites are not poolable, DerSimonian and Laird non-iterative random effects model [5] will be used to estimate the overall treatment effects (primary effectiveness and safety endpoints) as well the 90% confidence intervals treating sites as random effects.

9.4.6 Additional Analysis for Primary Effectiveness Endpoint

Univariate and multivariate logistic regression models will be used to examine the impact of the covariates on the primary effectiveness endpoint. If the sites are not poolable, then study site and operators will be treated as random effects in the regression model. All covariates included in the analysis will consist of the following:

	Definition/ Variables	Note
Demographics	• Age • Gender • Ethnicity • Race • Study Site	• Continuous variable (unit: year) • Male, Female • Hispanic/ Latino or not • Asian, Black, Caucasian, Other • Random Effect if sites not poolable
Medical History	• Diabetes • Hypertension • Structural heart disease • Atrial Flutter • Duration of AF history • Frequency of AF episodes	
Cardiac Medical History	• Previously tried Class I AADs • Previously tried Class II AADs • Previously tried Class III AADs • Previously tried Class IV AADs	• Class I: Disopyramide, Flecainide, Propafenone, Quinidine • Class II: (Beta-Blocker): Acebutolol, Atenolol, Metoprolol, Propranolol, Sotalol, and other Beta-Blocker • Class III: Amiodarone, Dofetilide • Class IV: Verapamil, Diltiazem
TTE Result	• Baseline left atrial dimension	
Ablation Procedure	• Repeated ablation procedure or not • Procedure success • Use of Isoproterenol • Use of Adenosine • Agilis Sheath • Other Sheath • Total procedure time • CF values • Average power • Average impedance • Average temperature • Total RF ablation time • Tag index value • Etc.	

The primary effectiveness endpoint will be the dependent variables and the covariates will be treated as independent variables. Univariate logistic regression models will be conducted for each of the potential predictors. A p-value <0.20 is to be used as the cut-off point for screening covariates. Forward model selection will be used to select predictors that remain significant at p-

value <0.05 in the multivariate model. Interaction terms may be examined based on those covariates that remain significant in the final model.

The analysis population of the additional analysis for the primary effectiveness endpoint will be the PP population. This analysis will only be performed after the 12 months follow-up is complete.

9.5 Analysis of Secondary Endpoints

No formal statistical hypothesis and inferential statistics will be formulated and performed for the secondary effectiveness and safety endpoints. Descriptive statistics including number and percentages of subjects/targets will be presented for each secondary endpoints. The number of events will also be presented. Secondary safety endpoints will be analyzed in the safety population. Secondary effectiveness endpoints will be analyzed in Full Set Effectiveness population.

9.6 Analysis of Additional Endpoints

No formal statistical hypothesis and inferential statistics will be formulated and performed for the additional effectiveness and safety endpoints. Additional endpoints will be analyzed in Full Set Effectiveness population.

9.6.1 Procedural Data

Descriptive statistics will be used to summarize and list the procedural data.

Specifically, the number and percentage of procedures that achieved the target tag index values vs. those that were stopped before reaching the target tag index values will be summarized and listed.

9.6.2 Quality of Life Data

The individual and summary score of SF-12 will be presented.

9.7 Analysis of Health Economic Data

Because this data does not support the safety and effectiveness of the STSF Catheter and the EPU, it will not be provided to the Food and Drug Administration (FDA) as part of the IDE reporting.

REFERENCES

1. Berry SM, Carlin, BP, Lee, JJ, and Mueller, P (2010) Bayesian Adaptive Methods for Clinical Trials, Chapman & Hall.

2. Wilber DJ, Pappone C, Neuzil P, De Paola A, Marchlinski F, Natale A, Macle L, Daoud EG, Calkins H, Hall B, Reddy V, Augello G, Reynolds MR, Vinekar C, Liu CY, Berry SM, Berry DA; ThermoCool AF Trial Investigators (2010) Comparison of antiarrhythmic drug therapy and radiofrequency catheter ablation in patients with paroxysmal atrial fibrillation: a randomized controlled trial. Journal of the American Medical Association;303(4):333-40.

3. Rubin D. Multiple Imputation for Nonresponse in Surveys, Section 5.4 2004

4. Yan X, Lee S, and Li N. Missing Data Handling Methods in Medical Device Clinical Trials. Journal of Biopharmaceutical Statistics, 19: 1085–1098, 2009

5. DerSimonian R and Laird N. Meta-Analysis in Clinical Trials. Controlled Clinical Trials 7:177-188 (1986).

6. Holmes DR, Monahan KH, Packer D, (2009) Pulmonary Vein Stenosis Complicating Ablation for Atrial Fibrillation. JACC Intv. 2:267-276

7. Oh Jk, Seward JB, Tajik AJ. The Echo Manual. Lippincott Williams & Wilkinds 2006, pp 143-153