Medtronic **Statistical Analysis Plan**	
Clinical Investigation Plan Title	DIAMOND- AF II Study Title: A Prospective Clinical Evaluation of the DiamondTemp™ Ablation System for the Treatment of Persistent Atrial Fibrillation
Clinical Investigation Plan Identifier	MDT20012 (TP01071)
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Sponsor/Local Sponsor	**Sponsor:** United States of America Medtronic, Inc. Cardiac Ablation Solutions 8200 Coral Sea Street NE Mounds View, MN 55112 USA +1-800-328-2518 Medtronic Sunnyvale - EPIX Therapeutics 945 Stewart Drive Suite 100 Sunnyvale, CA 94085 USA +1-408-470-4500 **Local Sponsors:** Canada Medtronic Canada ULC 99 Hereford Street Brampton, Ontario, L6Y 0R3, Canada +1-905-460-3800 Europe Medtronic, Bakken Research Center B.V. Endepolsdomein 5 6229 GW Maastricht, The Netherlands +31-43-3566566

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1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	Not Applicable, New Document	Shufeng Liu Senior Principal Statistician

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AAD	Anti-Arrhythmic Drugs
ADE	Adverse Device Event
AE	Adverse Event
AF	Atrial Fibrillation
AFEQT	Atrial Fibrillation Effect on Quality of Life
AFL	Atrial Flutter
AT	Atrial Tachycardia
CEC	Clinical Events Committee
CIP	Clinical Investigation Plan
CTI	Cavotricuspid Isthmus
CSR	Clinical Study Report
CVA	Cerebral Vascular Accident
ECG	Electrocardiogram
ICF	Informed Consent Form
ITT	Intention-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intention-to-Treat
OPC	Objective Performance Criterion
PeAF	Persistent Atrial Fibrillation
PP	Per Protocol
PT	Preferred Term
PV	Pulmonary Vein
PVI	Pulmonary Vein Isolation
RF	Radiofrequency
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
TIA	Transient Ischemic Attack
WHO	World Health Organization

3. Introduction

Atrial Fibrillation (AF) is the most common clinically significant cardiac arrhythmia and a major public health concern in the United States. AF is an abnormal heart rhythm that has been classified as

recurrent when two or more episodes are detected. Episodes of AF that are continuous and sustained beyond 7 days but less than 12 months are classified as persistent AF (PeAF) according to the most recent 2017 HRS/EHRA Consensus Statement. Of all electrophysiological mechanisms responsible for AF, of significant interest are the pulmonary veins (PVs) which have been identified to play a critical role in triggering and maintaining AF.

The purpose of the Diamond-AF II study is to demonstrate the safety and effectiveness of the DiamondTemp Ablation System for the treatment of drug refractory, symptomatic persistent AF. The study will focus on pulmonary vein isolation (PVI) being the "cornerstone" of PeAF ablation but will allow physicians to consider additional ablation strategies per their standard ablation practice and within the recommendations of the study protocol.

This statistical analysis plan (SAP) outlines the data and procedures used for assessing the efficacy and safety endpoints of Protocol TP01071: A Prospective Clinical Evaluation of the DiamondTemp™ Ablation System for the Treatment of Persistent Atrial Fibrillation. This SAP has been developed prior to database lock to further describe the statistical methods and planned analyses of the study data to be included in the clinical study report (CSR).

4. Study Objectives

Primary Safety Objective

To demonstrate that the primary safety event rate associated with the DiamondTemp ablation system is lower than the pre-specified Objective Performance Criterion (OPC).

Primary Effectiveness Objective

To demonstrate that the primary effectiveness rate associated with the DiamondTemp ablation system is higher than the pre-specified Objective Performance Criterion (OPC).

Secondary Objectives

1. To estimate the freedom from a composite of SAEs occurring within 30-days post-index ablation procedure as adjudicated by an independent CEC for relatedness to the procedure or device.
2. To estimate the freedom from documented AF/AFL/AT episodes during the effectiveness evaluation period lasting ≥ 30 seconds in duration by ECG monitoring.
3. To estimate the freedom from documented AF/AFL/AT episodes during the effectiveness evaluation period in the absence of class I and III anti-arrhythmic drug therapy.
4. To estimate the rate of acute procedural success.
5. To estimate the rate of single procedure success with freedom from AF/AFL/AT recurrence.
6. To estimate the rate of single procedure success with freedom from all primary effectiveness failure criteria.
7. To evaluate changes in QOL using the AFEQT Questionnaire.
8. To evaluate neurological changes measured using the NIH stroke scale.

Ancillary Objectives

1. To characterize procedural characteristics.

2. To characterize the number of re-hospitalizations due to Atrial Fibrillation recurrence during the effectiveness evaluation period.

5. Investigation Plan

The DIAMOND-AF II Study is a prospective, non-randomized (single-group assignment) trial being performed at multiple centers in the United States, Canada and Europe to evaluate the safety and effectiveness of the DiamondTemp Ablation System for the treatment of patients with persistent atrial fibrillation.

This study will enroll up to 376 subjects diagnosed with persistent AF at up to 30 investigational sites in the US, Canada and Europe. Investigational sites will have a principal investigator (PI) that is responsible for the conduct of a research study as well as sub-investigators. It is anticipated that approximately 50% of the subjects will be enrolled at centers within the United States. The maximum number of enrollments per site should not exceed 20%. Subjects will be followed for a minimum of 12 months post index ablation procedure.

6. Determination of Sample Size

For the primary safety endpoint, a sample size of 269 achieves 81% power to detect a difference of at least -4.5% using an Objective Performance Criterion (OPC) of 11.5% and a one-sided target level of significance of 0.025. Reference Section 7.9.1 for relevant statistical hypotheses.

Similarly, for the primary effectiveness endpoint, a sample size of 274 yields 86% power to detect a difference of 9% using an OPC of 40% and a one-sided target level of significance of 0.025. Reference Section 7.9.2 for relevant statistical hypotheses.

Assuming a drop-out rate of 12%, as well as accounting for eligibility/screen failures, the enrollment goal of up to 376 subjects should be sufficient.

7. Statistical Methods

7.1 Study Subjects

7.1.1 Disposition of Subjects

Subject disposition will be illustrated by a study flow diagram, detailing subject enrollment, treatment, follow-up, and attrition.

Inclusion and Exclusion criteria violations will be summarized, as well as follow-up compliance and reasons for premature study discontinuations. The number of subjects included in each of the analysis populations (as defined in Section 7.1.3) will be summarized.

7.1.2 Clinical Investigation Plan (CIP) Deviations

Protocol deviations will be summarized in the clinical study report by coded category. The number of deviations per category, and the number and percentage of subjects with a deviation in each category will be reported. A listing showing the protocol deviation details will also be provided.

7.1.3 Analysis Populations

Three analysis populations are defined for this study:

Intention-to-Treat Population

The Intention-to-Treat (ITT) population will be comprised of all subjects who sign Informed Consent Form (ICF) and attempt study treatment (i.e., catheter inserted into vasculature).

Modified Intention-to-Treat Population

The modified ITT (mITT) population will be a subset of the ITT population and comprised of all ITT subjects who meet eligibility criteria.

The primary effectiveness and safety analysis will be conducted using this mITT population.

Per Protocol Population

The Per Protocol (PP) population will be a subset of the mITT population and comprised of all mITT subjects who do not have any major protocol deviations (i.e., eligibility criteria violations, or ablation treatment with a non-study catheter for the index procedure or during blanking period).

All study objectives will be analyzed using the mITT population. Additionally, sensitivity analyses of the primary safety and effectiveness objectives will be performed using the ITT and PP populations.

7.2 General Methodology

The DIAMOND-AF II Study is a prospective, non-randomized (single-group assignment) trial being performed at multiple centers in the United States, Canada and Europe.

If applicable, the following general comments pertain to the statistical analyses and data presentations:

- All statistical analyses will be performed using a one-sided hypothesis test at the overall 2.5% level of significance. P-values will be rounded to three decimal places. If a p-value is less than 0.001 it will be reported as "< 0.001." If a p-value is greater than 0.999 it will be reported as "> 0.999." No adjustments for multiplicity are planned.
- Continuous data will be summarized using descriptive statistics: number of subjects, mean, standard deviation or standard error, median, minimum and maximum. The decision to use either standard deviation or standard error will be based upon the objective of the presentation: standard deviation will be used when the interest is the natural variability of the data; standard error will be used when comparing two or more means. Continuous variables that are recorded using approximate values (e.g., < or >) will be replaced by the closest exact value for the calculation of summary statistics.
- Nominal categorical variables will be summarized using frequency counts and percentages.
- Ordinal variables may be analyzed as if they were continuously scaled and a combination of the above may be employed as appropriate: frequency and percentage of observations within a category and means and standard deviations of the scores of the categories.
- For categorical and ordinal variables, percentages will be calculated based on non- missing data.
- Baseline is defined as the last measurement for the outcome of interest obtained before the exposure to the study device.
- Duration variables will be calculated using the general formula: (end date – start date)

- All tables and listings will have a header showing the Sponsor name ("Medtronic"), the protocol number and the page number with the total number of pages in the listing or table. A footer will show the data extraction date, the file name, path, the program run date, along with notes and definitions for abbreviations used in the tables and listings.
- Within-subject changes will be calculated as visit value minus baseline value such that a negative change reflects a decrease and a positive change signifies an increase. The paired sample t-test or Wilcoxon Signed Rank test may be used to test if the mean (or median) within-subject change is equal to zero.
- MedDRA Version 20.0 or higher will be used for coding of all adverse events; WHO-Drug may be used for coding concomitant medications.
- Version 9.2 or higher of SAS® statistical software package or other validated statistical software will be used to provide all summaries, listings, graphs, and statistical analyses.

7.3 Center Pooling

Study analysis will use pooled data from all contributing study sites and geographies.

To evaluate homogeneity of treatment effect (safety and effectiveness primary endpoints) across geographies, the log-rank test will be used to compare results across the two geographical regions: US/Canada and Europe.

7.4 Handling of Missing, Unused, and Spurious Data and Dropouts

All available data will be used in data listings and tabulations.

Missing data due to early dropout on the primary endpoints may occur if a subject receives study treatment but discontinues prematurely from the study without experiencing a primary safety or effectiveness failure event.

The main analysis of the primary objectives will use available data with no imputations for missing data, where subjects who discontinue prematurely will be censored at their last study contact date in the Kaplan-Meier analysis.

Additionally, to assess the potential impact of missing data due to early dropout on the primary objectives, a tipping point analysis will be performed where subjects who discontinue prematurely will be iteratively imputed as failures in the order of their censoring times. The tipping point is defined as the number of imputed failures when the one-sided 97.5% confidence bound of the endpoint estimate crosses the performance goal (11.5% for primary safety and 40% for primary effectiveness).

Analysis of the secondary and ancillary objectives and any other study data will use available data with no imputations for missing data.

7.5 Adjustments for Multiple Comparisons

No adjustment for multiple comparisons is needed or planned for this study.

The study will be considered successful when both the primary safety objective and the primary effectiveness objective are met. For each primary objective, the sample size ensures a power of at least 80% for a one-sided hypothesis test with alpha level of 0.025.

The secondary and ancillary study objectives will be analyzed descriptively without hypothesis testing, therefore adjustment for multiple comparisons is not applicable.

7.6 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized for the mITT Set. Demographic variables include age, sex, and geographic ancestry. Baseline characteristics include height, weight, BMI, and duration of disease.

Medical and Surgical History will be summarized for the mITT Set. Any past medical findings or surgical procedures will be summarized by Body System.

The pre-treatment physical exam will be summarized for the mITT Set. Any findings will be summarized by Body System.

7.7 Treatment Characteristics

Procedural characteristics of the DiamondTemp ablation treatment will be summarized as an ancillary objective.

All medications taken from the screening date up to the index procedure and after the index procedure through the last study visit will be summarized based on the World Health Organization (WHO) Drug dictionary.

7.8 Interim Analyses

No formal statistical interim analyses are planned for this study.

7.9 Evaluation of Objectives

All study objectives will be analyzed using the mITT population. Additionally, sensitivity analyses of the primary safety and effectiveness objectives will be performed using the ITT and PP populations.

The DIAMOND-AF II study will be considered successful when both the primary safety objective and the primary effectiveness objective are met.

7.9.1 Primary Safety Objective

Primary Safety Objective

To demonstrate that the primary safety event rate associated with the DiamondTemp ablation system is lower than the pre-specified Objective Performance Criterion (OPC).

Hypothesis

H_0: $P \geqslant P_0$

H_1: $P < P_0$

where P_0 = 11.5% (Safety OPC), and lower event rates are better.

Endpoint Definition and Derivation

The primary safety endpoint is defined as freedom from a composite of serious adverse events (SAEs) occurring within 7 days, procedure and/or device-related significant pericardial effusion that occurs within 30 days, and severe or clinically symptomatic pulmonary vein stenosis and atrioesophageal fistula through 6 months post-index ablation procedure, as adjudicated by an independent Clinical Events Committee (CEC) for relatedness to the procedure or device.

The primary safety device- or procedure-related SAE composite will be the combined rate of the following events:

- Atrioesophageal fistula
- Bleeding complication
- Cardiac tamponade / perforation
- Death
- Extended hospitalization
- Myocardial infarction
- Pericarditis
- Phrenic nerve paralysis
- Pulmonary edema
- Pulmonary vein stenosis
- Significant pericardial effusion
- Stroke / CVA
- Thromboembolism
- Transient ischemic attack (TIA)
- Vagal nerve injury
- Vascular access complications

Performance Requirements

The null hypothesis will be rejected if the one-sided 97.5% upper confidence bound of the primary safety event rate is lower than 11.5%.

Rationale for Performance Criteria

This performance goal was derived from a point estimate of 7% and a margin of indifference of 4.5%. This point estimate value was determined from a review of the FDA publicly available information combined with the published literature for all FDA approved medical device trials for Atrial Fibrillation treatment[1] and some other studies[2] on ablation treatment for Atrial Fibrillation. Based on the Sponsor's

[1] Reddy, et al. "Results of the TOCCASTAR Study," Circulation. Aug. 10, 2015. DOI 10.1161 CirculationAHA.114.014092
https://www.accessdata.fda.gov/cdrh_docs/pdf13/P130026b.pdf
Wilbur, et al. JAMA Vol. 303, No. 4. P333-340.
https://www.accessdata.fda.gov/cdrh_docs/pdf3/P030031S011b.pdf
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Dukkipati, et al. JACC Vol 66. No.12, 2015. p1350-1360.
https://www.accessdata.fda.gov/cdrh_docs/pdf10/P100010b.pdf
Natale, et al. JACC Vol.64, No.7, 2014. P 647- 656.

[2] Squara, et al. Europace (2015) 17, 718-724.
Kuck, Karl-Heinz, et al. NEJM 374;23, June 9, 2016, 2235-2245.
Chen, Yi-He et al. Europace (2017) 19, 784-794

best estimations, the overall rates of SAEs reported in these studies ranged from 4.9% to 14.6%, while most IDE approved randomized trials were designed to allow for 8% to 10% non-inferiority margins.

Analysis Methods

The components of the SAE composite endpoint will be summarized to show the number and percentage of subjects meeting each component.

The primary safety event rate will be calculated as 1 minus the survivor function (i.e., event freedom rate), which is obtained using the Kaplan-Meier method along with the log-log transformation to compute the two-sided 95% confidence interval. The null hypothesis will be rejected if the one-sided 97.5% upper confidence bound of the primary safety event rate is lower than 11.5%.

Additionally, a corresponding one-sided p-value may be constructed as follows. First compute the z-statistic using the below formula:

$$z = \frac{\log\left(-\log\left(S(t)\right)\right) - \log(-\log(0.885))}{\sqrt{\sigma(t)^2 \Big/ (S(t) * \log\left(S(t)\right))^2}}$$

Where S(t) is the Kaplan-Meier estimate of the survivor function (i.e., the primary safety event freedom rate) at 6 months (180 days) post index ablation, and $\sigma^2(t)$ is the Greenwood's estimate of the variance of the survivor function S(t) at time t. The one-sided p-value will then be computed from the standard normal distribution as P(Z<z), which is the area of the standard normal distribution less than z since log(-log(S(t))) will be less than log(-log(0.885)) if S(t) > 0.885 (i.e., event rate < 0.115).

The following subgroup analyses are prospectively defined: geography (US/Canada and Europe), gender (female and male), and age (≤65 and >65 years). The log-rank test will be used to test homogeneity of the primary safety endpoint results between the subgroups.

Determination of Subjects/Data for Analysis

The main analysis of the primary safety objective will be based on the mITT population, which includes all subjects who sign informed consent, meet eligibility criteria and attempt study treatment (i.e., catheter inserted into vasculature). Additionally, sensitivity analysis for the primary safety objective will be conducted on the Per-Protocol population, which includes all mITT subjects who do not have any major protocol violations (i.e., eligibility criteria violations, or ablation treatment with a non-study catheter), and the ITT population, which includes all subjects who sign informed consent and attempt study treatment.

7.9.2 Primary Effectiveness Objective

Primary Effectiveness Objective

To demonstrate that the primary effectiveness rate associated with the DiamondTemp ablation system is higher than the pre-specified Objective Performance Criterion (OPC).

Hypothesis

H_0: $P \leqslant P_0$

H_1: $P > P_0$

where P_0 = 40% (Effectiveness OPC), and higher effectiveness rates are better.

Endpoint Definition and Derivation

The primary effectiveness endpoint is defined as freedom from documented Atrial Fibrillation (AF), Atrial Flutter* (AFL) and Atrial Tachycardia (AT) episodes following the blanking period (3-month follow-up post-ablation procedure) through the end of the effectiveness evaluation period (12-month follow-up post-ablation procedure).

An effectiveness failure is defined by any of the following events:

- Inability to electrically isolate all accessible targeted pulmonary veins during the ablation procedure.
- Documented episodes of AF, AFL or AT lasting ≥ 30 seconds in duration as evidenced by electrocardiographic data during the effectiveness evaluation period.
- DC cardioversion for AF, AFL or AT during the effectiveness evaluation period.
- A repeat ablation procedure to treat AF, AFL or AT during the effectiveness evaluation period.
- Use of a new or previously failed anti-arrhythmic drug (AAD) at a dose greater than the highest ineffective dose for AF during the effectiveness evaluation period.
- Use of a non-study device for ablation of any AF targets during the index or repeat ablation procedure during the blanking period.
- More than one (1) repeat ablation procedure during the blanking period.

** Occurrence and/or ablation of cavotricuspid isthmus (CTI)-dependent AFL, as confirmed by entrainment maneuvers during EP testing at any time during this study is not a primary effectiveness failure because it is not considered an iatrogenic arrhythmia following a left atrial ablation procedure for AF.*

The blanking period for a subject starts on the date of the index ablation procedure (day 0) and ends on day 90 post index ablation.

The effectiveness evaluation period for a subject starts on day 91 post index ablation and ends on the study exit date or day 410 post index ablation (i.e., close of the 12-month visit window), whichever is earlier.

If a primary effectiveness failure event occurs post day 365 and within the effectiveness evaluation period, the date of the event will be set to day 365 so that these events will be accounted for in the 12-month Kaplan-Meier estimate of the primary effectiveness endpoint.

Performance Requirements

The null hypothesis will be rejected if the one-sided 97.5% lower confidence bound of the primary effectiveness rate is greater than 40%.

Rationale for Performance Criteria

The performance goal was derived based on the minimum 12-month success rate for persistent AF recommended in the 2017 HRS Expert Consensus Statement on Catheter and Surgical Ablation of AF.

Analysis Methods

The components of the primary effectiveness composite endpoint will be summarized to show the number and percentage of subjects meeting each component.

The primary effectiveness rate will be analyzed using the Kaplan-Meier method with the log-log transformation to compute the two-sided 95% confidence interval. The null hypothesis will be rejected if the one-sided 97.5% lower confidence bound of the primary effectiveness rate is greater than 40%.

Additionally, a corresponding one-sided p-value may be constructed as follows. First compute the z-statistic using the below formula:

$$z = \frac{\log\left(-\log\left(S(t)\right)\right) - \log(-\log(0.4))}{\sqrt{\sigma(t)^2 \Big/ (S(t) * \log\left(S(t)\right))^2}}$$

Where S(t) is the Kaplan-Meier estimate of the primary effectiveness rate at 12 months (365 days) post index ablation, and $\sigma^2(t)$ is the Greenwood's estimate of the variance of the survivor function S(t) at time t. The one-sided p-value will then be computed from the standard normal distribution as P(Z<z), which is the area of the standard normal distribution less than z since log(-log(S(t))) will be less than log(-log(0.4)) if S(t) > 0.4.

The following subgroup analyses are prospectively defined: geography (US/Canada and Europe), gender (female and male), and age (≤65 and >65 years). The log-rank test will be used to test homogeneity of the primary effectiveness endpoint results between the subgroups.

Determination of Subjects/Data for Analysis

The main analysis of the primary effectiveness objective will be based on the mITT population, which includes all subjects who sign informed consent, meet eligibility criteria and attempt study treatment (i.e., catheter inserted into vasculature). Additionally, sensitivity analysis for the primary effectiveness objective will be conducted on the Per-Protocol population, which includes all mITT subjects who do not have any major protocol violations (i.e., eligibility criteria violations, or ablation treatment with a non-study catheter), and the ITT population, which includes all subjects who sign informed consent and attempt study treatment.

7.9.3 Secondary Objectives

The secondary objectives will further characterize the performance of the DiamondTemp Ablation System. All secondary endpoints will be analyzed descriptively. Analysis of all secondary objectives will use available data with no imputations for missing data, and the percentage of missing data will be displayed for each analysis.

7.9.3.1 Secondary Objective #1

Objective

To estimate the freedom from a composite of SAEs occurring within 30-days post-index ablation procedure as adjudicated by an independent CEC for relatedness to the procedure or device.

Endpoint Definition and Derivation

The SAE composite endpoint is comprised of the same types of events as defined for the primary safety endpoint but occurring within 30 days post index ablation.

Analysis Methods

This secondary endpoint will be analyzed using the Kaplan-Meier method with the log-log transformation to compute the two-sided 95% confidence interval. The components of the SAE composite endpoint will also be summarized to show the number and percentage of subjects meeting each component.

Determination of Subjects/Data for Analysis

All subjects in the mITT population will be included in the analysis.

7.9.3.2 Secondary Objective #2

Objective

To estimate the freedom from documented AF/AFL/AT episodes during the effectiveness evaluation period lasting ≥ 30 seconds in duration by ECG monitoring.

Endpoint Definition and Derivation

A subject is considered a failure for this endpoint if he/she has any documented AF/AFL/AT episode ≥ 30 seconds by ECG monitoring during the effectiveness evaluation period.

Analysis Methods

This secondary endpoint will be analyzed using the Kaplan-Meier method with the log-log transformation to compute the two-sided 95% confidence interval.

Determination of Subjects/Data for Analysis

All subjects in the mITT population will be included in the analysis.

7.9.3.3 Secondary Objective #3

Objective

To estimate the freedom from documented AF/AFL/AT episodes during the effectiveness evaluation period in the absence of class I and III anti-arrhythmic drug therapy.

Endpoint Definition and Derivation

A subject is considered a failure for this endpoint if he/she has any documented AF/AFL/AT episode and/or uses any class I/III AAD during the effectiveness evaluation period.

Analysis Methods

This secondary endpoint will be analyzed using the Kaplan-Meier method with the log-log transformation to compute the two-sided 95% confidence interval.

Determination of Subjects/Data for Analysis

All subjects in the mITT population will be included in the analysis.

7.9.3.4 Secondary Objective #4

Objective

To estimate the rate of acute procedural success.

Endpoint Definition and Derivation

An acute procedural success is defined as confirmation of electrical isolation of PVs at least 20 minutes following the last ablation around the respective PV.

Analysis Methods

This secondary endpoint will be analyzed using the Binomial method and an exact 95% confidence interval will be constructed.

Determination of Subjects/Data for Analysis

All subjects in the mITT population will be included in the analysis. The analysis will be based on index ablation procedures only.

7.9.3.5 Secondary Objective #5

Objective

To estimate the rate of single procedure success with freedom from AF/AFL/AT recurrence.

Endpoint Definition and Derivation

A subject is considered a single procedure success if he/she is treated with one single ablation procedure during study participation and free from documented AF/AFL/AT episode at 12 months post index ablation.

Analysis Methods

This secondary endpoint will be analyzed using the Kaplan-Meier method with the log-log transformation to compute the two-sided 95% confidence interval.

Determination of Subjects/Data for Analysis

All subjects in the mITT population will be included in the analysis.

7.9.3.6 Secondary Objective #6

Objective

To estimate the rate of single procedure success with freedom from all primary effectiveness failure criteria.

Endpoint Definition and Derivation

A subject is considered a single procedure success if he/she is treated with one single ablation procedure during study participation and free from all primary effectiveness failure criteria at 12 months post index ablation.

Analysis Methods

This secondary endpoint will be analyzed using the Kaplan-Meier method with the log-log transformation to compute the two-sided 95% confidence interval.

Determination of Subjects/Data for Analysis

All subjects in the mITT population will be included in the analysis.

7.9.3.7 Secondary Objective #7

Objective

To evaluate changes in QOL using the AFEQT Questionnaire.

Endpoint Definition and Derivation

Subject's QOL is measured using the AFEQT Questionnaire at baseline, 6-month visit and 12-month visit. The QOL change from baseline to 6 months, as well as change from baseline to 12 months will be calculated for each subject.

Analysis Methods

This secondary endpoint will be analyzed using descriptive statistics.

Determination of Subjects/Data for Analysis

All subjects in the mITT population will be included in the analysis.

7.9.3.8 Secondary Objective #8

Objective

To evaluate neurological changes measured using the NIH stroke scale.

Endpoint Definition and Derivation

Subject's neurological function is measured using the NIH stroke scale at baseline, pre-discharge visit and 12-month visit. The neurological change from baseline to pre-discharge, as well as change from baseline to 12 months will be calculated for each subject.

Analysis Methods

This secondary endpoint will be analyzed using descriptive statistics.

Determination of Subjects/Data for Analysis

All subjects in the mITT population will be included in the analysis.

7.9.4 Ancillary Objectives

The ancillary objectives will further characterize the performance of the DiamondTemp Ablation System. All ancillary endpoints will be analyzed descriptively. Analysis of all ancillary objectives will use available data with no imputations for missing data, and the percentage of missing data will be displayed for each analysis.

7.9.4.1 Ancillary Objective #1

Objective

To characterize procedural characteristics.

Endpoint Definition and Derivation

The following procedure characteristics will be summarized for all index ablation procedures:

- Total procedure time (minutes), defined as time of investigational catheter insertion into the vasculature to time of last ablation catheter removal.
- Total treatment device time (minutes), defined as time of delivery of first RF ablation with the investigational catheter to removal of the catheter.
- Mean cumulative RF Time (minutes).
- Mean duration of RF ablations (seconds).
- Total fluid infused through the investigational catheter (mL).
- Total fluoroscopy time (minutes).

Analysis Methods

This ancillary endpoint will be analyzed using descriptive statistics.

Determination of Subjects/Data for Analysis

All subjects in the mITT population will be included in the analysis. The analysis will be based on index ablation procedures only.

7.9.4.2 Ancillary Objective #2

Objective

To characterize the number of re-hospitalizations due to Atrial Fibrillation recurrence during the effectiveness evaluation period.

Endpoint Definition and Derivation

The number of re-hospitalizations due to Atrial Fibrillation recurrence during the effectiveness evaluation period will be calculated for each subject.

Analysis Methods

This ancillary endpoint will be analyzed using descriptive statistics.

Determination of Subjects/Data for Analysis

All subjects in the mITT population will be included in the analysis.

7.10 Safety Evaluation

Adverse event classifications and definitions are described in the Clinical Investigational Plan.

An overall summary of adverse events will be presented to include the number and percentage of subjects who report at least one adverse event, the total number of adverse events, the number of adverse events and the number and percentage of subjects who report adverse events by seriousness and relationship to the study treatment (i.e., study ablation procedure or device). For events adjudicated by the CEC, the CEC classifications will be used in the analysis; in cases where only the investigator classifies the event, the investigator's classification will be used.

The frequencies and percentages of adverse events will be presented by MedDRA system organ class (SOC) and preferred term (PT). The frequencies and percentages of AEs judged to be at least possibly related to study treatment will be presented by MedDRA SOC and PT. Similar tables will be presented for the subset of serious adverse events (SAEs).

Complete subject listings of all adverse events, all SAEs, and all AEs at least possibly related to study treatment will be provided. For each adverse event the following details will be specified: start and stop dates, event description, MedDRA SOC and PT, relationship to study ablation device, relationship to study ablation procedure, actions taken, outcome of the adverse event and seriousness (yes/no).

A summary table of all deaths will be compiled to summarize death classification and relationship to study treatment. A detailed listing of all deaths will also be provided.

A detailed listing of all reported device deficiencies will be provided.

7.11 Changes to Planned Analysis

This SAP has been developed prior to database lock to further describe the statistical methods and planned analyses of the study data to be included in the clinical study report. Any change to the data analysis methods described in the CIP will require a CIP amendment only if it changes a principal feature of the CIP. Any other change to the data analysis methods described in the CIP or SAP, and the justification for making the change, will be described in the clinical study report.

8. Validation Requirements

All data analyses for the clinical study report (CSR) will be validated. Levels of validation required for the different elements of the CSR are specified in the table below.

Validation Level	Definition	Required for
Level I	A peer reviewer independently programs output and then compares the output with that generated by the original author of the program to be validated	All analyses in the CSR pertaining to the primary safety and primary effectiveness objectives of the study
Level II *	A peer reviewer reviews the program, and where appropriate, performs calculations or programming checks to verify the output	All other analyses in the CSR *

*At a minimum, Level II validation will be performed.