Pivotal Study Of A Dual Epicardial & Endocardial Procedure (DEEP) Approach for Treatment of Subjects with Persistent or Long Standing Persistent Atrial Fibrillation with Radiofrequency Ablation

DEEP Pivotal Study

Trial Number: CP2014-1

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Statistical Analysis Plan

Version 2.0, 25Jul2023

Version History

Version	Version Date	Author/Title	Summary of Key Changes
1.0	06DEC2022	Chris Mullin	Initial Release
2.0	25JUL2023	Joe Derr	Updated populations to align with Protocol Rev. H Added Modified Intent to Treat (mITT) Population

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Table of Contents

1 Introduction

This statistical analysis plan (SAP) describes the planned statistical methods to be used during the reporting and analysis of data collected under the Clinical Study Protocol CP2014-1 DEEP Pivotal Study. This SAP should be read in conjunction with the study clinical study plan (CSP) and case report forms (CRFs). This version of the SAP has been developed with respect to the Clinical Study Protocol CP2014-1 DEEP Pivotal Study Revision H 28Sep2022. Any revisions to the protocol or CRFs that impact the planned analyses may require updates to the SAP.

2 Study Objectives

The primary objective of this study is to evaluate the safety and effectiveness of a dual epicardial and endocardial ablation procedure for patients presenting with Persistent Atrial Fibrillation or Longstanding Persistent Atrial Fibrillation utilizing the AtriCure Bipolar System and AtriClip PRO LAA Exclusion System in an endoscopic or open ablation procedure, followed by an endocardial mapping and ablation procedure utilizing commercially available RF based, ablation catheters.

The effectiveness of the device will be demonstrated by establishing that the device effectively eliminates persistent and long-standing persistent atrial fibrillation, atrial flutter, or atrial tachycardia in a clinically significant proportion of treated patients.

2.1 Study Endpoints

The study has one primary effectiveness endpoint, one primary safety endpoint, eight secondary effectiveness endpoints, eight secondary safety endpoints, and four secondary health economics endpoints.

2.1.1 Primary Effectiveness Endpoint

The primary effectiveness endpoint is freedom from any documented AF, atrial flutter, or atrial tachycardia lasting >30 seconds in duration through the 12-month follow-up visit in the absence of Class I or III AADs (with the exception of previously failed AADs at doses not exceeding those previously failed).

Any arrhythmia that occurs within the blanking period or the AAD Optimization period will not be considered a failure (Visit 5 up to Visit 10). The rhythm status used for evaluation of this endpoint will be derived from regularly scheduled monitoring (i.e. Holter, Zio™-Patch, or 30 second ECG) as well as any symptom driven monitoring that is performed.

The following scenarios shall constitute a failure of the primary effectiveness endpoint:

1. Any documented AF, atrial flutter, or atrial tachycardia lasting >30 seconds duration that occurs at any time beginning at the 6-month visit and through the 12-month visit. These will be

documented on any Core Lab – ECG form with a time interval of "6 Month Post Endocardial" or "12 Month Post Endocardial".

2. Any previously failed class I or III AAD administered at a dose higher than baseline and between the 6-month visit date plus one day and the 12-month visit date.
3. Any newly introduced class I or III AAD usage beginning at the 6-month visit date plus one day and through the 12-month visit date.
4. DC cardioversion for AF, atrial flutter, or atrial tachycardia that takes place at any time beginning at the 6-month visit date and ending at the 12-month visit date.
5. Catheter ablation or surgical treatment for AF, atrial flutter, atrial tachycardia that takes place at any time beginning at the 3-month visit date and ending at the 12-month visit date.
6. Two or more repeat catheter ablations within the 2nd blanking period.
7. The use of a non-AtriCure study device for creation of any lesions during the surgical epicardial ablation procedure.

For the purposes of this study, atrioventricular nodal reentrant tachycardia (AVNRT), inappropriate sinus tachycardia, and Wolff–Parkinson–White syndrome (WPW) will not be considered procedure failures.

For this study, AtriCure defines failure of an antiarrhythmic drug (AAD) to include ineffectiveness or intolerance of the AAD.

2.1.2 Primary Safety Endpoint

The primary safety endpoint is a composite endpoint consisting of any one or more of the following events if they are adjudicated by the CEC to be serious adverse events (SAEs) and related to device/procedures as follows:

1. The AtriCure Bipolar System and/or the AtriClip Pro LAA Exclusion System, within 30 days following the epicardial surgical ablation procedure; or
2. The epicardial surgical ablation procedure within 30 days following the epicardial procedure; or
3. The endocardial index procedure (or a repeat endocardial ablation procedure performed during the blanking period) within 7 days following an endocardial ablation procedure.

Events except as otherwise specified for a particular condition include:

a. death (regardless of cause)
b. stroke
c. transient ischemic attack (TIA)

d. myocardial infarction (MI)

e. pulmonary or systemic embolism

f. pericarditis resulting in an effusion that leads to hemodynamic compromise or requires pericardiocentesis, prolongs hospitalization by more than 48 hours, requires a new hospitalization, or persists for more than 30 days following the ablation procedure

g. excessive bleeding, defined as one or more of the following:

   i. re-operation to control bleeding within 7 days post-epicardial surgical procedure; or surgery to control bleeding within 7 days post-endocardial ablation procedure, if related to the device or procedure;

   ii. receipt of ≥ 2 units of blood transfused in a 24-hour period during the first 7 days post-epicardial surgical procedure, or within the first 7 days post-endocardial ablation procedure, if related to the device or procedure;

   iii. conversion to sternotomy or thoracotomy that requires ≥ 2 units blood to be transfused, or performed to treat hypotension, cardiac arrest, or repair of a cardiac injury.

h. wound infection at surgical site requiring re-operation for wound debridement

i. atrio-esophageal fistula (from the time of surgical procedure through 12-month follow-up visit)

j. permanent phrenic nerve paralysis, defined as paralysis that remains unresolved at the 12-month follow-up visit

k. permanent pacemaker implantation that is a direct result of injury to the specialized conduction system (SA node or AV node) during the epicardial surgical ablation procedure.

l. pulmonary vein (PV) stenosis of >70%, as measured at any time after the endocardial catheter ablation procedure through the 12-month follow-up period

m. major vascular access complications, including the development of a hematoma, an arteriovenous fistula, or a pseudoaneurysm requiring intervention such as surgical repair or transfusion, prolongs the hospital stay, or requires a new hospital admission

2.1.3 Secondary Efficacy Endpoints

1. Exclusion of the LAA, defined as lack of fluid communication (<3 mm residual communication with LAA and < 10mm residual pocket) between the LA and LAA. This endpoint will be measured at the 12-month Visit (Visit 11). The AtriClip® effectiveness population will be utilized for this analysis endpoint.
2. Exclusion of the LAA, defined as lack of fluid communication (<3 mm residual communication with LAA and <10 mm residual pocket) between the LA and LAA. The endpoint will be measured at the intra-procedurally (Visit 2), at the Endocardial EP Ablation Procedure (Visit 5). The AtriClip effectiveness population will be utilized for this analysis endpoint.
3. Acute procedural success of epicardial surgical procedure, defined as the percentage of subjects with successful electrical isolation/block of all pulmonary veins, as well as the “box”.
4. Acute procedural success of endocardial catheter procedure, defined as the percentage of subjects with successful electrical isolation/block of all pulmonary veins and the “box”, as well as bi-directional block of the cavo-tricuspid isthmus.
5. Freedom from Atrial Fibrillation, Atrial Tachycardia, Atrial Flutter without AAD, defined as no documented event >30 seconds in duration (or for the entire length of an ECG tracking) with no utilization of AADs beyond the blanking and AAD optimization periods, except as previously failed without an increase in dose. This endpoint will be measured through the 12-month, 2, 3, 4, and 5-year visits (Visits 11-15) via continuous 24- hour ECG monitor.
6. Freedom from Atrial Fibrillation, Atrial Tachycardia, Atrial Flutter regardless of AAD, defined as no documented event >30 seconds in duration (or for the entire length of a 30 second ECG tracing) regardless of AAD usage. This endpoint will be measured through the 12-month, 2, 3, 4, and 5-year visits (Visits 11-15 via continuous 24-hour ECG monitor).
7. Freedom from any documented AF, atrial flutter, or atrial tachycardia lasting >10 minutes in duration through the 12-month follow-up visit in the absence of Class I or III AADs (with the exception of previously failed AADs at doses not exceeding those previously failed).
8. Change in Quality of Life, defined as the total AFEQT score measured at the 12-month follow-up visit minus the score at the baseline visit. The score will be calculated per the AFEQT scoring manual.

2.1.4 Secondary Safety Endpoints

All secondary safety endpoints are supplemental and intended to provide a more complete picture of the overall safety profile for the DEEP procedure. They will not be tested for labeling purposes.

1. Major surgical events – This will be a composite safety endpoint within 30 days of the epicardial surgical procedure, as otherwise defined in the primary safety endpoint.
2. Major catheter events – This will be a composite safety endpoint within 7 days of the endocardial catheter procedure, as otherwise defined in the primary safety endpoint.
3. 30-day surgical SAEs – This will include all SAEs that occur within 30 days of the epicardial surgical procedure and that are adjudicated to be related to the device or to the procedure.
4. 12-month DEEP SAEs – This will include all SAEs through the 12-month follow-up visit that are adjudicated to be related to an AtriCure device or to either stage of the DEEP procedure.
5. Unresolved SAEs – This will include all SAEs through the 12-month follow-up visit that are adjudicated to be related to an AtriCure device or to either stage of the DEEP procedure and that are not fully resolved by the 12-months visit. These events shall include any procedure related deaths, strokes with residual disability, unresolved phrenic nerve damage, or other such events that are adjudicated to have resulted in chronic disability or permanent damage.
6. Any serious adverse event through the 12-month follow-up visit, regardless of attribution.
7. Incidence of stroke or TIA at 12-month, 24, 36, 48, 60-month visits.
8. Any esophageal injury that meets all of the following criteria: identified post epicardial ablation, adjudicated by core lab to be a thermal injury with perforation, and related to an AtriCure ablation device, through 30-days post epicardial procedure.

2.1.5 Secondary Health Economics Endpoints

All health economics endpoints are exploratory in nature.

1. Utilization of cardioversion, defined as the number of cardioversion events (visits) that a subject had in the past 12-month period. This endpoint will be measured at the 12-month, 2, 3, 4, and 5-year (Visits 11- 15) follow-up visits.
2. Hospital readmissions for AF, atrial flutter, or atrial tachycardia, defined as the number of readmissions in the past 12-month period. This endpoint will be measured at the 12-month, 2, 3, 4, and 5-year (Visits 11- 15) follow-up visits.
3. Total length of stay for all hospital readmissions for AF, atrial flutter, or atrial tachycardia, defined as the sum of the length of stay for each such visit within the last 12-month period. This endpoint will be measured at the 12-month, 2, 3, 4, and 5-year (Visits 11-15) follow-up visits.
4. Emergency Room Visits for AF, atrial flutter, or atrial tachycardia, defined as the number of visits in the past 12-month period. This endpoint will be measured at the 12-month, 2, 3, 4, and 5-year (Visits 11-15) follow-up visits.

3 Study Design

The study is a prospective, multicenter, single arm, pivotal study.

4 Sample Size Determination

The study is planned for up to 220 subjects and up to 35 sites (30 US and 5 OUS). Details regarding sample size determination are provided in the CSP.

5 Statistical Analyses

5.1 General Considerations

Except where otherwise specified, the following general principles apply to the planned statistical analyses. All statistical analysis will be conducted using SAS version 9.4 or later (SAS Institute Inc., Cary, NC) or other widely-accepted statistical or graphical software as required.

5.1.1 Descriptive Statistics

Continuous data will be summarized with mean, standard deviation, median, minimum, maximum, and number of evaluable observations. Categorical variables will be summarized with frequency counts and percentages. Confidence intervals may be presented, where appropriate, using the t-distribution for continuous data and Clopper-Pearson Exact method for categorical variables unless specified otherwise.

5.1.2 Study Day

Study day 0 is the date of the index procedure. Day in study will be calculated relative to the index procedure as follows:

Study Day = Assessment Date – Index Procedure Date

For each subject, duration in study will be based on last study contact date which is the latest date of all follow-up visits, assessments, adverse event onset or resolution, and study exit including date of death.

Duration variables will be calculated as follows:

Duration Days = End Date – Index Procedure Date

5.1.3 Visit Windows

Unless otherwise specified, visit based assessments will be analyzed for each analysis time point according to the nominal visit entered in the Case Report Form (CRF) regardless of if it is out of window.

5.2 Analysis Populations

Intent to treat patient population (ITT): The ITT subject population will include all subjects who have met all inclusion/exclusion criteria and on whom a procedure was attempted (defined as a subject who underwent induction of anesthesia).

Modified intent to treat patient population (mITT): The mITT subject population will include all subjects who attempted the Epicardial Procedure (defined as a subject who underwent induction of anesthesia) and have at least one post-procedure follow-up visit after the 2nd Blanking Period (with the 2nd blanking period defined as the 90-days post Endocardial Ablation Procedure) with non-missing primary effectiveness data.

Safety Population: The safety population will include all enrolled subjects that undergo induction of anesthesia.

Per protocol patient population (PP): The PP patient population will include all subjects who complete both the Epicardial Surgical Ablation Procedure and Endocardial EP Ablation Procedure.

AtriClip Effectiveness population: The AtriClip effectiveness population will include all ITT subjects for whom an attempt (entrance of the AtriClip into the chest wall) is made to place an AtriClip device.

The primary effectiveness analysis will utilize the mITT patient population as defined in this statistical analysis plan. The analysis will be repeated on the ITT and PP patient populations as supportive analyses. Secondary effectiveness analyses will be conducted on the mITT, the ITT and the PP patient populations. All safety analyses will utilize the safety population.

5.3 Handling of Missing Data

All safety analysis will utilize the safety population and no missing values will be imputed unless a subject misses a follow-up visit and cannot subsequently be contacted to determine their primary safety status. In this case, the primary safety endpoint will be considered a failure and the subject will be excluded from any subsequent secondary safety analyses for which their status is unknown. If a procedure is aborted due to a primary safety event, the subject will be considered a safety failure. If a subject misses a follow up visit, but it can be subsequently verified that the subject did not incur a safety failure, the subject will be considered a success. As an additional analysis, the primary safety endpoint will be analyzed based on only observed failures, with all other subjects in the Safety Population counting as a success.

The primary effectiveness analysis will utilize the mITT population and the LOCF method for missing values, as defined below. A subject with any primary effectiveness failure from the 6-month visit

through the 12-month visit will be considered a failure for all methods below. Any subjects who withdraw or are lost-to-follow-up after the 6-months visit (post AAD optimization) but prior to the 12-month follow-up visit, or for any reason do not have 12-month ECG readings available, will be analyzed as follows:

1) Last observation carried forward (LOCF): Any subject who is missing a scheduled testing will be considered an effectiveness success or failure at that scheduled visit based on their status up to and including their last testing.
2) Worst case: Any subject with no primary effectiveness failure recorded and with no 12-month test data will be considered a failure.
3) Best case: Any subject with no primary effectiveness failure recorded and with no 12-month test data will be considered a success.
4) Break-even: If the study endpoint is met using the best-case methodology and is not met using the worst-case methodology, a break-even analysis will be performed to determine the number of subjects with missing endpoint data who would be required to be a success in order to meet the endpoint.

All secondary endpoints for LAA exclusion will utilize the LOCF method for missing values. No missing values will be imputed for the remaining secondary endpoints. If a subject is missing a value for one of these secondary endpoints, they will not be included in the analysis of that endpoint. The number of patients with non-missing values will be reported for each endpoint.

5.4 Subject Disposition

The number of subjects in each analysis population will be presented along with reason for any exclusions. Subject accountability will be summarized by visit. The number of subjects who are enrolled, eligible for follow-up, and number completing clinical follow-up will be summarized for each protocol-required visit. In addition, the number of subjects who complete the study or exit early will be summarized by reason.

5.5 Demographics and Baseline Characteristics

Descriptive statistics will be presented for all clinically relevant baseline demographic, medical history, and clinical characteristic variables.

5.6 Analysis of Study Endpoints

The study will be considered successful if both the primary effectiveness and primary safety endpoints are statistically significant at the 0.025 level (one-sided).

5.6.1 Primary Effectiveness Endpoint

The primary effectiveness endpoint is freedom from any documented AF, atrial flutter, or atrial tachycardia lasting >30 seconds in duration through the 12-month follow-up visit in the absence of Class I or III AADs (with the exception of previously failed AADs at doses not exceeding those previously failed). Effectiveness failure events are described in detail in section 2.1.1.

5.6.1.1 Primary Analysis

The statistical analysis of the primary effectiveness endpoint will consist of a comparison of the proportion of patients who remain a primary effectiveness success at the 12-month visit to a historical control rate that is based on results from the feasibility trials and published literature. The primary effectiveness endpoint will be assessed with the following hypothesis:

$$H_0: p_E \leq 0.60$$

$$H_a: p_E > 0.60$$

where p_E = the proportion of primary effectiveness success. The hypothesis will be evaluated using a one-sided chi-squared test at a one-sided α=0.025 level of significance. The objective will be met if the estimated one-sided p-value is < 0.025. The mITT population will be the primary population for this analysis. Missing values will be treated as described in the Missing Values section 5.3 with the primary method being the LOCF method.

The proportion of primary effectiveness successes will be calculated with subjects as the experimental unit (i.e., the subject will be considered a success if no primary effectiveness failure was recorded from the 6-month visit through the 12-month visit). The numerator of the proportion will be the number of subjects who are a primary effectiveness success, and the denominator will be the total number of subjects. The endpoint will be presented with the numerator and denominator, the proportion and its 95% two-sided exact binomial confidence interval, and the one-sided p-value.

5.6.1.2 Sensitivity Analysis

Sensitivity analyses for the primary effectiveness are discussed in the sections of this SAP related to missing data (different imputation schemes) and analysis populations (i.e., PP analysis).

5.6.2 Primary Safety Endpoint

The primary safety endpoint is a composite endpoint consisting of any one or more of events described in section 2.1.2 if they are adjudicated by the CEC to be serious adverse events (SAEs) and related to device/procedures.

5.6.2.1 Primary Analysis

The statistical analysis of the primary safety endpoint will consist of a comparison of the proportion of patients who fail to complete the trial without a primary safety endpoint event to a historical control rate that is based on results from the feasibility trials. Adverse events will be adjudicated in accordance with the CSP. The primary safety endpoint will be assessed with the following hypothesis:

$$H_0: p_s \geq 0.28$$

$$H_a: p_s < 0.28$$

where p_s = the proportion of primary safety failures in the safety population. The hypothesis will be evaluated using a one-sided statistical test using the normal approximation to the binomial distribution. A Z-test will be conducted at a one-sided α=0.025 level of significance to test the hypothesis. The objective will be met if the estimated one-sided p-value is < 0.025. The safety population will be the primary population for this analysis. Missing values will be treated as described in the Missing Values section 5.3. If a subject misses a follow-up visit and cannot subsequently be contacted to determine their primary safety status, the primary safety endpoint will be considered a failure and the subject will be excluded from any subsequent secondary safety analyses for which their status is unknown.

The proportion of primary safety failures will be calculated with subjects as the experimental unit (i.e., the subject will be considered a failure if a primary safety event was experienced within the timeframes defined in the endpoint). The numerator of the proportion will be the number of subjects who have a primary safety event and the denominator will be the total number of subjects. The endpoint will be presented with the numerator and denominator, the proportion and its 95% two-sided normal approximated confidence interval, and the one-sided p-value.

5.6.3 Secondary Effectiveness Endpoints

Analysis of secondary effectiveness endpoints will be based on descriptive statistics and nominal two-sided 95% confidence intervals for observed data, with methods as described in section 5.1.1. Secondary Effectiveness Endpoint #1 will be evaluated with a hypothesis test. The remaining secondary endpoints will be presented as exploratory analyses; no statistical inference will be performed.

5.6.3.1 Secondary Effectiveness Endpoint #1

The statistical analysis of secondary effectiveness endpoint #1 will consist of a comparison of the proportion of patients with LAA exclusion at the 12 Month Visit is statistically significantly higher than 80%, which will exceed the 77.5% expectation of success based on other exclusion methods, with less risk of injury than those methods. The primary effectiveness endpoint will be assessed with the following hypothesis:

$$H_0: p_2 \leq 0.80$$

$$H_a: p_2 > 0.80$$

where p_2 = the proportion of subjects with LAA exclusion at the 12-month Visit. LAA exclusion is defined as a lack of fluid communication (<3 mm residual communication with LAA and < 10mm residual pocket) between the LA and LAA. The hypothesis will be evaluated using a one-sided statistical test. An exact, one-sample binomial test will be conducted at a one-sided α=0.025 level of significance to test the hypothesis. The objective will be met if the estimated one-sided p-value is < 0.025. The AtriClip effectiveness population will be the primary population for this analysis. The LOCF method will be utilized for patients who do not have TEE testing at the 12-Month visit.

The proportion will be calculated with subjects as the experimental unit. The numerator of the proportion will be the number of subjects with LAA exclusion at the 12-month Visit and the denominator will be the total number of subjects. The endpoint will be presented with the numerator and denominator, the proportion and its 95% two-sided exact binomial confidence interval, and the one-sided p-value.

5.6.3.2 Secondary Effectiveness Endpoint #2

The statistical analysis of secondary effectiveness endpoint #2 will consist of an estimate of the proportion of patients with LAA exclusion intra-procedurally (Visit 2) and at the Endocardial EP Ablation Procedure (Visit 5). The AtriClip effectiveness population will be the population for this analysis. Missing observations will be excluded.

The proportion will be calculated with subjects as the experimental unit. The numerator of the proportion will be the number of subjects with LAA exclusion at the Visit and the denominator will be the total number of subjects without a missing observation. LAA exclusion is defined as a lack of fluid communication (<3 mm residual communication with LAA and < 10mm residual pocket) between the LA and LAA. The endpoint will be presented separately for Visits 2 and 5 with the numerator and denominator, the proportion and its 95% two-sided exact binomial confidence interval.

5.6.3.3 Secondary Effectiveness Endpoint #3

The statistical analysis of secondary effectiveness endpoint #3 will consist of an estimate of the proportion of patients with acute procedural success of epicardial surgical procedure, defined as the percentage of subjects with successful electrical isolation/block of all pulmonary veins, as well as the "box". The ITT and PP populations will be used for this analysis. Missing observations will be excluded.

The proportion will be calculated with subjects as the experimental unit. The numerator of the proportion will be the number of subjects with acute procedural success and the denominator will be the total number of subjects without a missing observation. The endpoint will be presented for each analysis population with the numerator and denominator, the proportion and its 95% two-sided exact binomial confidence interval.

5.6.3.4 Secondary Effectiveness Endpoint #4

The statistical analysis of secondary effectiveness endpoint #4 will consist of an estimate of the proportion of patients with acute procedural success of endocardial catheter procedure, defined as the percentage of subjects with successful electrical isolation/block of all pulmonary veins and the "box", as well as bi-directional block of the cavo-tricuspid isthmus. The mITT, ITT and PP populations will be used for this analysis. Missing observations will be excluded.

The proportion will be calculated with subjects as the experimental unit. The numerator of the proportion will be the number of subjects with acute procedural success and the denominator will be the total number of subjects without a missing observation. The endpoint will be presented for each analysis population with the numerator and denominator, the proportion and its 95% two-sided exact binomial confidence interval.

5.6.3.5 Secondary Effectiveness Endpoint #5

The statistical analysis of secondary effectiveness endpoint #5 will consist of an estimate of the proportion of patients with freedom from Atrial Fibrillation, Atrial Tachycardia, Atrial Flutter without AAD, defined as no documented event >30 seconds in duration (or for the entire length of an ECG tracking) with no utilization of AADs beyond the blanking and AAD optimization periods, except as previously failed without an increase in dose. This endpoint will be measured through the 12-month, 2, 3, 4, and 5-year visits (Visits 11-15) via cumulative 24- hour ECG monitor. The mITT, ITT and PP populations will be used for this analysis. Missing observations will be excluded.

The proportion will be calculated with subjects as the experimental unit. The numerator of the proportion will be the number of subjects with freedom from the aforementioned events and the denominator will be the total number of subjects without a missing observation. The endpoint will be presented through each visit for each analysis population with the numerator and denominator, the proportion and its 95% two-sided exact binomial confidence interval. A similar summary will be provided for each yearly visit; if a subject fails at a given year they will be counted as a failure for subsequent yearly visits.

5.6.3.6 Secondary Effectiveness Endpoint #6

The statistical analysis of secondary effectiveness endpoint #6 will consist of an estimate of the proportion of patients with freedom from Atrial Fibrillation, Atrial Tachycardia, Atrial Flutter regardless of AAD, defined as no documented event >30 seconds in duration (or for the entire length of a 30 second ECG tracing) regardless of AAD usage. This endpoint will be measured through the 12-month, 2, 3, 4, and 5-year visits (Visits 11-15 via cumulative 24-hour ECG monitor). The mITT, ITT and PP populations will be used for this analysis. Missing observations will be excluded.

The proportion will be calculated with subjects as the experimental unit. The numerator of the proportion will be the number of subjects with freedom from the aforementioned events and the denominator will be the total number of subjects without a missing observation. The endpoint will be presented through each visit for each analysis population with the numerator and denominator, the proportion and its 95% two-sided exact binomial confidence interval. A similar summary will be provided for each yearly visit; if a subject fails at a given year they will be counted as a failure for subsequent yearly visits.

5.6.3.7 Secondary Effectiveness Endpoint #7

The statistical analysis of secondary effectiveness endpoint #7 will consist of an estimate of the proportion of patients with freedom from any documented AF, atrial flutter, or atrial tachycardia lasting >10 minutes in duration through the 12-month follow-up visit in the absence of Class I or III AADs (with the exception of previously failed AADs at doses not exceeding those previously failed). The mITT, ITT and PP populations will be used for this analysis. Missing observations will be excluded.

The proportion will be calculated with subjects as the experimental unit. The numerator of the proportion will be the number of subjects with freedom from the aforementioned events and the denominator will be the total number of subjects without a missing observation. The endpoint will be presented for each analysis population with the numerator and denominator, the proportion and its 95% two-sided exact binomial confidence interval.

5.6.3.8 Secondary Effectiveness Endpoint #8

The statistical analysis of secondary effectiveness endpoint #8 will consist of an estimate of the change in Quality of Life, defined as the total AFEQT score measured at the 12-month follow-up visit minus the score at the baseline visit. The score will be calculated per the AFEQT scoring manual. The mITT, ITT and PP populations will be used for this analysis. Missing observations will be excluded.

The difference in scores will be calculated with subjects as the experimental unit. The mean difference of AFEQT scores will be presented for each analysis population with its 95% confidence interval using the t-distribution. The standard deviation, median, minimum, maximum, and number of evaluable observations will also be presented.

5.6.4 Secondary Safety Endpoints

All secondary safety endpoints are supplemental and intended to provide a more complete picture of the overall safety profile for the DEEP procedure. They will not be tested for labeling purposes. Analysis of secondary safety endpoints will be based on descriptive statistics and nominal two-sided 95% confidence intervals for observed data, with methods as described in section 5.1.1. All secondary safety endpoints will be presented as exploratory analyses; no statistical inference will be performed.

5.6.4.1 Secondary Safety Endpoint #1

The statistical analysis of secondary safety endpoint #1 will consist of an estimate of the proportion of patients with a major surgical event. This will be a composite safety endpoint within 30 days of the epicardial surgical procedure, as otherwise defined in the primary safety endpoint events described in section 2.1.2. The safety population will be used for this analysis. Missing observations will be excluded.

The proportion will be calculated with subjects as the experimental unit. The numerator of the proportion will be the number of subjects with a major surgical event and the denominator will be the total number of subjects without a missing observation. The endpoint will be presented with the numerator and denominator, the proportion and its 95% two-sided exact binomial confidence interval.

5.6.4.2 Secondary Safety Endpoint #2

The statistical analysis of secondary safety endpoint #2 will consist of an estimate of the proportion of patients with a major catheter event. This will be a composite safety endpoint within 7 days of the endocardial catheter procedure, as otherwise defined in the primary safety endpoint events described in section 2.1.2. The safety population will be used for this analysis. Missing observations will be excluded.

The proportion will be calculated with subjects as the experimental unit. The numerator of the proportion will be the number of subjects with a major catheter event and the denominator will be the total number of subjects without a missing observation. The endpoint will be presented with the numerator and denominator, the proportion and its 95% two-sided exact binomial confidence interval.

5.6.4.3 Secondary Safety Endpoint #3

The statistical analysis of secondary safety endpoint #3 will consist of an estimate of the proportion of patients with a surgical SAEs within 30 days of surgery. This will include all SAEs that occur within 30 days of the epicardial surgical procedure and that are adjudicated to be related to the device or to the procedure. The safety population will be used for this analysis. Missing observations will be excluded.

The proportion will be calculated with subjects as the experimental unit. The numerator of the proportion will be the number of subjects with a surgical SAE and the denominator will be the total number of subjects without a missing observation. The endpoint will be presented with the numerator and denominator, the proportion and its 95% two-sided exact binomial confidence interval.

5.6.4.4 Secondary Safety Endpoint #4

The statistical analysis of secondary safety endpoint #4 will consist of an estimate of the proportion of patients with DEEP SAEs within 12-months. This will include all SAEs through the 12-month follow-up visit that are adjudicated to be related to an AtriCure device or to either stage of the DEEP procedure. The safety population will be used for this analysis. Missing observations will be excluded.

The proportion will be calculated with subjects as the experimental unit. The numerator of the proportion will be the number of subjects with a DEEP related SAE and the denominator will be the total number of subjects without a missing observation. The endpoint will be presented with the numerator and denominator, the proportion and its 95% two-sided exact binomial confidence interval.

5.6.4.5 Secondary Safety Endpoint #5

The statistical analysis of secondary safety endpoint #5 will consist of an estimate of the proportion of patients with an unresolved SAE. This will include all SAEs through the 12-month follow-up visit that are adjudicated to be related to an AtriCure device or to either stage of the DEEP procedure and that are not fully resolved by the 12-months visit. These events shall include any procedure-related deaths, strokes with residual disability, unresolved phrenic nerve damage, or other such events that are adjudicated to have resulted in chronic disability or permanent damage. The safety population will be used for this analysis. Missing observations will be excluded.

The proportion will be calculated with subjects as the experimental unit. The numerator of the proportion will be the number of subjects with an unresolved SAE and the denominator will be the total number of subjects without a missing observation. The endpoint will be presented with the numerator and denominator, the proportion and its 95% two-sided exact binomial confidence interval.

5.6.4.6 Secondary Safety Endpoint #6

The statistical analysis of secondary safety endpoint #6 will consist of an estimate of the proportion of patients with any SAE through 12-months. This is defined as any serious adverse event through the 12-month follow-up visit, regardless of attribution. The safety population will be used for this analysis. Missing observations will be excluded.

The proportion will be calculated with subjects as the experimental unit. The numerator of the proportion will be the number of subjects with an SAE and the denominator will be the total number of subjects without a missing observation. The endpoint will be presented with the numerator and denominator, the proportion and its 95% two-sided exact binomial confidence interval.

5.6.4.7 Secondary Safety Endpoint #7

The statistical analysis of secondary safety endpoint #7 will consist of an estimate of the incidence of stroke or TIA at 12-month, 2, 3, 4, and 5-year visits (Visits 11-15). The safety population will be used for this analysis. Missing observations will be excluded.

The numerator of the proportion will be the number of stroke or TIA events and the denominator will be the total number of subject years ($\frac{\#\ Subjects \times Visit\ Month}{12\ Months}$) for subjects without a missing observation. The endpoint will be presented through each specified visit for each analysis population with the numerator and denominator, the incidence rate and its 95% two-sided exact Poisson confidence interval.

5.6.4.8 Secondary Safety Endpoint #8

The statistical analysis of secondary safety endpoint #8 will consist of an estimate of the proportion of patients with any esophageal injury through 30-days post epicardial procedure. This will include all esophageal injuries that meets all of the following criteria: identified post epicardial ablation, adjudicated by core lab to be a thermal injury with perforation, and related to an AtriCure ablation device. The safety population will be used for this analysis. Missing observations will be excluded.

The proportion will be calculated with subjects as the experimental unit. The numerator of the proportion will be the number of subjects with an esophageal injury and the denominator will be the total number of subjects without a missing observation. The endpoint will be presented with the numerator and denominator, the proportion and its 95% two-sided exact binomial confidence interval.

5.6.5 Secondary Health Economics Endpoints

All health economics endpoints are exploratory in nature; no statistical inference will be performed. Analysis of secondary health economics endpoints will be based on descriptive statistics and nominal two-sided 95% confidence intervals for observed data, with methods as described in section 5.1.1.

5.6.5.1 Secondary Health Economics Endpoint #1

The statistical analysis of secondary health economics endpoint #1 will consist of an estimate of the utilization of cardioversion, defined as the number of cardioversion events (visits) that a subject had in the past 12-month period. This endpoint will be measured at the 12-month, 2, 3, 4, and 5-year (Visits 11-15) follow-up visits. The mITT, ITT and PP populations will be used for this analysis. Missing observations will be excluded.

The numerator of the proportion will be the number of cardioversion events and the denominator will be the total number of subjects without a missing observation. The endpoint will be presented for each specified visit window for each population with the numerator and denominator, the incidence rate and its 95% two-sided exact Poisson confidence interval.

5.6.5.2 Secondary Health Economics Endpoint #2

The statistical analysis of secondary health economics endpoint #2 will consist of an estimate of the hospital readmissions for AF, atrial flutter, or atrial tachycardia, defined as the number of readmissions in the past 12-month period. This endpoint will be measured at the 12-month, 2, 3, 4, and 5-year (Visits 11- 15) follow-up visits. The mITT, ITT and PP populations will be used for this analysis. Missing observations will be excluded.

The numerator of the proportion will be the number of hospital readmissions and the denominator will be the total number of subjects without a missing observation. The endpoint will be presented for each

specified visit window for each population with the numerator and denominator, the incidence rate and its 95% two-sided exact Poisson confidence interval.

5.6.5.3 Secondary Health Economics Endpoint #3

The statistical analysis of secondary health economics endpoint #3 will consist of an estimate of the total length of stay (LOS) for all hospital readmissions for AF, atrial flutter, or atrial tachycardia, defined as the sum of the length of stay for each such visit within the last 12-month period. This endpoint will be measured at the 12-month, 2, 3, 4, and 5-year (Visits 11-15) follow-up visits. The mITT, ITT and PP populations will be used for this analysis. Missing observations will be excluded.

The LOS over the previous 12-months will be evaluated with subjects as the experimental unit. The mean LOS will be presented for each specified visit window for each population with its 95% confidence interval using the t-distribution. The standard deviation, median, minimum, maximum, and number of evaluable observations will also be presented.

5.6.5.4 Secondary Health Economics Endpoint #4

The statistical analysis of secondary health economics endpoint #4 will consist of an estimate of the incidence of Emergency Room Visits for AF, atrial flutter, or atrial tachycardia, defined as the number of visits in the past 12-month period. This endpoint will be measured at the 12-month, 2, 3, 4, and 5-year (Visits 11-15) follow-up visits. The mITT, ITT and PP populations will be used for this analysis. Missing observations will be excluded.

The numerator of the proportion will be the number of emergency rooms visits and the denominator will be the total number of subjects without a missing observation. The endpoint will be presented for each specified visit window for each population with the numerator and denominator, the incidence rate and its 95% two-sided exact Poisson confidence interval.

5.7 Poolability Analyses

Primary safety and effectiveness endpoints will be reported by site, by region (US and OUS), by gender, and by classification of persistent AF (longstanding vs. non-longstanding). In addition, logistic regression models will be utilized to test for statistically significant differences in the endpoints due to site, region (US and OUS) gender, and classification of persistent AF (longstanding vs. non-longstanding), while also adjusting for age, BMI, baseline comorbid conditions, LVEF, total length of AF, and number of previous catheter ablations. If adjusting for covariates causes problems of model fitting, tests for interactions may need to be made with Firth's penalized likelihood approach or via models omitting covariates used for adjustment. P-values will be reported for each covariate and odds ratios with 95% confidence intervals will be reported for gender and for classification of persistent AF.

This overall goal of this study is to show safety and effectiveness in a representative population of patients with persistent atrial fibrillation and thus it is not powered for separate analysis of individual subpopulations.

5.8 Subgroup Analyses

No subgroup analyses are planned beyond those specified in section 5.7.

5.9 Interim Analyses

There are no interim analyses planned.

5.10 Protocol Deviations

Deviations from the procedures outlined in the CSP will be reported by investigational sites on the CRF. Protocol deviations will be summarized for all deviations and by type (i.e. deviation code) with total deviation counts and number of subjects with at least one deviation. A listing of all protocol deviations will be provided that includes details of each deviation (e.g. deviation reason, justification/corrective action, etc).

6 Changes from Planned Analyses

Any changes to planned statistical analyses determined necessary prior to performing the analyses will be documented in an amended Statistical Analysis Plan and approved prior to the analysis when possible. Any other deviations or changes from the planned analyses deemed necessary due to violation of critical underlying statistical assumptions, data characteristics, or missing data will be clearly described in the clinical study report with justification and rationale.

7 Subject Listings

Subject listings will be provided for the primary and secondary endpoints.