Statistical Analysis Plan

PROSPECTIVE EVALUATION OF OPEN IRRIGATED ABLATION CATHETERS WITH HIGH RESOLUTION MAPPING TO TREAT PAROXYSMAL ATRIAL FIBRILLATION

INTTERRUPT AF-PM009

CONFIDENTIAL

Revision History

Document Revision Number	Section	Change	Reason for Change
A.1		Initial Release	

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1 PROTOCOL SUMMARY

1.1 Study objective

To obtain data for the Rhythmia™ Mapping System in conjunction with Boston Scientific Open-Irrigated (OI) Catheters for ablation of Paroxysmal Atrial Fibrillation (PAF) according to current international and local guidelines.

Primary objective: To assess acute and long-term outcomes for the Rhythmia Mapping System in conjunction with Boston Scientific Open-Irrigated Ablation Catheters to treat de novo Paroxysmal Atrial Fibrillation. De Novo PAF is defined as subjects undergoing first ablation procedure for PAF with no prior left atrial ablation (RF, Cryo, Surgical).

1.2 Study devices

The study will include the following Boston Scientific Open-Irrigated Catheters in geographies where commercially approved for PAF ablation:

- Blazer Open-Irrigated Ablation Catheter
- IntellaNav Open-Irrigated Ablation Catheter
- IntellaNav MiFi Open-Irrigated Ablation Catheter
- IntellaTip MiFi Open-Irrigated Ablation Catheter
- Rhythmia Mapping System Gen 1 or Rhythmia HDx, equipped with Software 1.4 or any successive commercially approved versions.
- IntellaMap Orion Catheter

1.3 Study design

INTERRUPT AF study is a prospective, non-randomized, multicenter (global), post approval clinical study (PAS).

All subjects fitting the enrollment criteria, signing the consent and undergoing the index procedure with the study devices will be followed up for three years to complete the PAS design mandated from the FDA to collect post-market data for Boston Scientific Open-Irrigated Catheters and will be followed for three years.

1.4 Follow-up visits

Study follow-up visits include Enrollment, Baseline, Index Procedure, Pre-Discharge, 1 Month, 3 Months, 6 Months,12 Months, 24 Months, 36 Months and additional follow-up visits (including potential repeat procedures).

1.5 Planned number of sites and patients

The study will enroll 415 global subjects (US, EU, Asia-Pacific) with 25-50 centers. A minimum of 50% of the enrolling sites will be selected from the US. No study site will be allowed to contribute more than 41 subjects (10% of total allowed).

2 PURPOSE OF STATISTICAL ANALYSIS PLAN

The statistical analysis plan described in this document is to provide endpoint related analysis details to supplement the statistical methods provided in the INTERRUPT AF protocol.

3 ENDPOINTS AND ENDPOINT ANALYSES

This study has primary endpoints designed to assess the safety and effectiveness of the Boston Scientific family of Open-Irrigated Catheters in the general population of subjects undergoing de novo ablation for PAF. The study will be considered successful if both the primary safety and primary effectiveness endpoints are passed.

3.1 Primary Safety Endpoint

Safety will be evaluated by the primary safety event free rate at 12 months post procedure. Primary safety events will consist of a composite of acute primary safety events (events occurring within seven days post-procedure or hospital discharge, whichever is later), and chronic primary safety events (events occurring through 3 or 12 months post-procedure).

Acute primary safety events will be defined as the following:

- Death
- Myocardial infarction (MI)
- Vagal Nerve Injury/Gastroparesis
- Transient ischemic attack (TIA)
- Stroke/Cerebrovascular accident (CVA)
- Thromboembolism
- Pericarditis
- Cardiac tamponade/perforation
- Pneumothorax
- Vascular access complications
- Pulmonary edema/heart failure
- AV block

Chronic primary safety events will be defined as the following:

- Occurring through 3 Months post-procedure
    - Atrial esophageal fistula

- Pericardial effusion
- Occurring through 12 Months post-procedure
  - Pulmonary vein stenosis (symptomatic and requiring intervention)

3.1.1 Hypotheses

The primary safety objective is to demonstrate that the primary safety event-free rate through 12 months post-procedure is greater than the specified performance goal.

H_o: The primary safety event-free rate at 12 months post-procedure ≤ 85%[24, 25]

H_a: The primary safety event-free rate at 12 months post -procedure > 85%

3.1.2 Sample size

The sample size estimate was obtained using the normal approximation to the binomial distribution and verified through simulations based on Kaplan-Meier methodology. The following assumptions were used in the sample size calculation:

Assumptions	Primary Safety
Expected rate	90%[26]
Performance goal	85%
Attrition (per year)	7.5%
Significance level (one-sided)	5%
Power	80%

Under the hypothesis and assumptions outlined above, the required sample size for this endpoint is 329 TREATMENT subjects.

3.1.3 Statistical methods

For the primary safety endpoint, the Kaplan-Meier 12 month (365-day) primary safety event-free rate will be calculated. Subjects who withdraw from the study prior to 12 months without experiencing an event will be censored on the date of withdrawal. The 95% one-sided lower confidence limit of the observed safety event-free rate will be compared to the performance goal of 85%. If the lower confidence limit is greater than the performance goal, the null hypothesis will be rejected. The lower confidence limit will be calculated as the pointwise confidence limit using the log-log methodology.

3.2 Primary Effectiveness Endpoint

The primary effectiveness endpoint will be evaluated by the primary effectiveness event-free rate at 12 months post-procedure.

Primary effectiveness events will be defined as the following:

- Acute procedural failure
- More than one repeat procedure during the blanking period (90 days post index procedure)
- Documented atrial fibrillation, or new onset of atrial flutter or atrial tachycardia event (≥ 30 seconds in duration from an event monitor or Holter Monitor, or from a 10 second 12-lead EKG) between 91 days and 365 days post index procedure
- Any of the following interventions for atrial fibrillation, or new onset of atrial flutter or atrial tachycardia between 91 days and 365 days post index procedure:
  - Repeat procedure
  - Cardioversion
  - Prescribed any AAD*

  *AADs for endpoint will consist of all Class I/III and any Class II/IV medications taken for control of AF/AT/AFL recurrence

3.2.1 Hypotheses

The primary effectiveness objective is to demonstrate that the primary effectiveness event-free rate through 12 months post-procedure is greater than the specified performance goal.

H_0: The primary effectiveness event-free rate at 12 months post-procedure ≤ 50%[27]

H_a: The primary effectiveness event-free rate at 12 months post-procedure > 50%

3.2.2 Sample Size

The sample size estimate was obtained using the normal approximation to the binomial distribution and verified through simulations based on Kaplan-Meier methodology. The following assumptions were used in the sample size calculation:

Assumptions	Primary Effectiveness
Expected rate	60%[26,28,29]
Performance goal	50%
Attrition (per year)	7.5%
Significance level (one-sided)	5%
Power	80%

Under the hypothesis and assumptions outlined above, the required sample size for this endpoint is 183 TREATMENT subjects.

3.2.3 Statistical Methods

For the primary effectiveness endpoint, the Kaplan-Meier 12 month (365-day) primary effectiveness event-free rate will be calculated. Subjects who die or withdraw from the study prior to 12 months without experiencing an endpoint event will be censored on the date of death or the date of withdrawal. The 95% one-sided lower confidence limit of the observed primary effectiveness event-free rate will be compared to the performance goal of 50%. If the lower confidence limit is greater than the performance goal, the null hypothesis will be rejected. The lower confidence limit will be calculated as the pointwise confidence limit using the log-log methodology.

3.3 Secondary Effectiveness Endpoint

The secondary effectiveness endpoint is defined as the event-free at 12 months post-procedure.

Secondary effectiveness events are defined as:

- Acute procedural failure
- More than one repeat procedure during the blanking period (90 days post index procedure)
- Documented symptomatic atrial fibrillation, or new onset of atrial flutter or atrial tachycardia event (≥ 30 seconds in duration from an event monitor or Holter, or from a 10 second 12-lead EKG) between 91 days and 365 days post index procedure
- Any of the following interventions for atrial fibrillation, or new onset of atrial flutter or atrial tachycardia between 91 days and 365 days post index procedure:
    - Repeat procedure
    - Cardioversion
    - Prescribed a higher dose of any AAD* documented at baseline
    - Prescribed a new AAD* not documented at baseline

*AADs for endpoint will consist of all Class I/III and any Class II/IV medications taken for control of AF/AT/AFL recurrence

3.3.1 Hypotheses

The secondary effectiveness objective is to demonstrate that the secondary effectiveness event-free rate through 12 months post procedure is greater than the specified performance goal.

H_o: The secondary effectiveness event-free rate at 12 months post-procedure ≤ 50%

H_a: The secondary effectiveness event-free rate at 12 months post-procedure > 50%

3.3.2 Sample Size

The sample size estimate was obtained using the normal approximation to the binomial distribution and verified through simulations based on Kaplan-Meier methodology. The following assumptions were used in the sample size calculation:

Assumptions	Secondary Effectiveness
Expected rate	65%[26]
Performance goal	50%
Attrition (per year)	7.5%
Significance level (one-sided)	5%
Power	80%

Under the hypothesis and assumptions outlined above, the required sample size for this endpoint is 83 TREATMENT subjects.

3.3.3 Statistical Methods

For the secondary effectiveness endpoint, the Kaplan-Meier 12 month (365-day) secondary effectiveness event-free rate will be calculated. Subjects who die or withdraw from the study prior to 12 months without experiencing an event will be censored on the date of death or the date of withdrawal. The 95% one-sided lower confidence limit of the observed secondary effectiveness event-free rate will be compared to the performance goal of 50%. If the lower confidence limit is greater than the performance goal, the null hypothesis will be rejected. The lower confidence limit will be calculated as the pointwise confidence limit using the log-log methodology.

3.4 Tertiary endpoint

Chronic Effectiveness: Evaluation of chronic recurrence at 24 months and 36 months

- Recurrence is defined as intervention for atrial fibrillation, or new onset of atrial flutter or atrial tachycardia (repeat procedures, use of AADs, cardioversion), excluding repeat procedures during the 90-day blanking period.
- Data collection to include the diagnostic modality used to identify recurrence and the therapeutic intervention
- Chronic effectiveness will be evaluated using Kaplan-Meier methodology. The Kaplan-Meier 24 month and 36 month chronic recurrence-free rate will be calculated and presented along with the 95% confidence interval, calculated as the pointwise confidence limit using the log-log methodology Subjects who die or withdraw from the study prior to the specified time point without experiencing an event will be censored on the date death or on the date of withdrawal.

Center Experience: Primary safety and Primary effectiveness outcomes by center experience

- In order to evaluate training effectiveness for investigators outside of the ZERO AF IDE study, outcomes in centers performing five or more procedures using the Blazer OI catheter during the ZERO AF IDE study will be compared to all other. Kaplan-Meier rates and 95% confidence intervals for the Primary Safety and Effectiveness endpoints for both groups will be presented with no statistical comparison.

Safety: Reportable Adverse Events rates at 12, 24 and 36 months

Adverse events will be collected at all subject follow-up visits. Reportable events include:

- All Serious Adverse Events
- All Study Procedure-Related Adverse Events
- All Study Device-Related Adverse Events
- All Study Device Deficiencies
- Unanticipated Adverse Device Effects/Unanticipated Serious Adverse Device Effects previously not defined in the Directions For Use.

Adverse event rates will be calculated using binomial methodology. The cumulative number of events and event rate will be included in all study reports. Subjects at risk for an adverse event will be determined by the subject treatment status; all treatment and attempt subjects will be considered at risk for study related adverse events

Effectiveness: Acute Procedural Success Rate

Acute Procedural Success is defined as pulmonary vein isolation achieved with a Boston Scientific OI ablation catheter as demonstrated by map-based entrance block with exit block and other maneuvers (such as adenosine testing) at the discretion of the physician.

4 GENERAL STATISTICAL METHOD

4.1 Analysis Sets

While each endpoint was individually powered, each endpoint analysis will use all available data from all eligible subjects, regardless of original calculated sample size.

4.2 Control of Systematic Error/Bias

Selection of patients will be made from the Investigator's usual patient load. All patients meeting the eligibility criteria and having signed the ICF will be eligible for enrollment in the study.

4.3 Study Success and Control of Type I Error

Each primary endpoint can be tested at the significance level of 5% while still maintaining the overall type I error level at no greater than 5%. This follows the methodology of the Intersection-Union Test (IUT). If both primary endpoints are passed then a gating approach will be employed to test the secondary effectiveness endpoint at a significance level of 5%.

4.4 Number of Subjects per Investigative Site

To avoid any center effect and bias, one center will not be authorized to enroll more than 41 subjects (10% of the 415 enrollment total).

5 ADDITIONAL DATA ANALYSES

5.1 Interim Analyses and Progress Report Content

No formal interim analyses are planned for the purpose of stopping the study early for declaring effectiveness or for futility. Analysis of each endpoint will be performed when all applicable data for that endpoint has been collected. Analysis of the 12-month endpoints (Primary Safety, Primary Effectiveness, Secondary Effectiveness and all additional analyses pertaining to these endpoints) will be included in a Primary Endpoint Report. Additionally, Kaplan-Meier analyses for the Primary Safety Endpoint events using all available data at the time of the report will be included in interim progress reports to the FDA. These analyses will use the same definition of safety events used in the Primary Safety Endpoint but will censor active subjects who have not experienced an endpoint event and have not completed their 12-month follow-up on the day of the data snapshot.

Progress reports will be provided to the FDA every 6 months for the first two years and annually thereafter. Reports will include sections outlined in the relevant FDA guidance pertaining to Post Approval Studies. At minimum, the progress reports will contain the following:

- Number of study sites with enrolled subjects
- Summary of subject enrollment, subject status, and demographics
- Analysis of Primary Safety Endpoint events
- Summary of adverse events, deaths, deviations, and device deficiencies

Results from the progress reports will be posted on the FDA PAS website (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma_pas.cfm).

Field Code Changed

5.2 Subgroup Analyses

An analysis will be performed for the primary endpoints to determine whether significant differences exist in endpoint results between subgroups. The list of covariates (with applicable subgroups in parentheses) includes the following:

- Sex (Female vs. Male)
- Age at time of consent (subjects > 60 years vs subjects ≤60 years and subjects > 70 years vs subjects ≤70)
- Repeat procedures in the blanking period (Repeat procedure within 90 days of index procedure vs. no repeat procedure within 90 days of index procedure)
- Ablation technique (PVI only vs. PVI + additional ablations)
- Use of device features (DirectSense used in the index procedure vs DirectSense not used in the index procedure).

Each subgroup covariate will be included as a single independent variable in a logistic regression model with the primary endpoint outcome as the dependent variable and a test for significance at the 15% level will be performed.

5.3 Center Pooling Analysis

Center-to-center heterogeneity will be assessed for the primary endpoints by performing a random effects logistic regression analysis. Centers with less than five enrollments will be combined to form "supercenters". Small centers will be combined until the newly created supercenter has five enrollments, and then a new supercenter will be created. Centers will be deemed to be heterogeneous if the variance of the random center effect is found to significantly differ from zero. A significance level of 15% will be used for this test.

5.4 Catheter Type Pooling Analysis

Heterogeneity of outcomes by catheter type will be assessed for the primary endpoints by performing a logistic regression analysis with the primary endpoint outcome as the dependent variable and Catheter Type as the independent variable. Outcomes for the Blazer OI/IntellaNav OI catheters will be deemed to be heterogeneous with outcomes for the IntellaTip MiFi OI/IntellaNav MiFi OI catheters if no statistical association is found between catheter type and the primary endpoint outcomes through the logistic models. A significance level of 15% will be used for this test.

5.5 Additional Analyses

An analysis will be done for each primary endpoint stratifying results by catheter type (Blazer OI/IntellaNav OI and IntellaTip MiFi OI/IntellaNav MiFi OI).

Additional analyses will also be done to characterize the procedural workflow data in AF ablation cases with the Rhythmia Mapping System. Procedural workflow data will include, but not be limited to:

- electro-anatomical mapping information
- ablation gap detection (including gap detection techniques)
- ablation techniques (including use of DirectSense)

5.6 Sensitivity Analyses

5.6.1 Sensitivity analysis for the primary safety endpoint analysis

The sensitivity analysis -- tipping point analyses will be performed in order to characterize the impact of missing data on the main primary safety endpoint outcome by determining the point at which events in these subjects could have impacted the primary safety endpoint outcome. For the primary safety tipping point analysis, the overall cohort will consist of all Treatment and Attempt subjects. Tipping point analyses will be performed using the exact binomial distribution.

Tipping Point Analysis – Only subjects with complete data (subjects experienced the primary safety endpoint event or patients followed through 12 months) will be considered to have full follow-up data. All subjects with missing data (Subjects who withdraw before 12 months without experiencing an endpoint event will be classified as having missing data) will one by one be considered to have experienced an endpoint event. The rate and one-sided Clopper-Pearson lower 95% confidence bound will be calculated and lower confidence bound compared to the performance goal of 85%. The number of missing data subjects who would have needed to experience an event for the endpoint to be failed will be considered the tipping point for this analysis.

5.6.2 Sensitivity analysis for the primary effectiveness endpoint analysis

The sensitivity analysis -- tipping point analyses will be performed in order to characterize the impact of missing data on the main primary effectiveness endpoint outcome by determining the point at which events in missing data subjects could have impacted the primary effectiveness outcome. For the primary effectiveness tipping point analysis, the overall cohort will consist of all Treatment subjects. The analysis will be performed using the exact binomial distribution.

Tipping Point Analysis– Only subjects with complete data (subjects experienced the primary effectiveness endpoint event or patients followed through 12 months) will be considered to have full follow-up data. Subjects with missing data (Subjects who withdraw or die before 12 months without experiencing an endpoint event will be classified as having missing data) will one by one be considered to have experienced an endpoint event. The rate and one-sided Clopper-Pearson lower 95% confidence bound will be calculated and lower confidence bound compared to the performance goal of

50%. The number of missing data subjects who would have needed to experience an event for the endpoint to be failed will be considered the tipping point for this analysis.

5.7 DIRECTSENSE subject related analysis

Additional analysis will be performed on data from all subjects where the DIRECTSENSE feature was used for their index procedure. Refer to the DIRECTSENSE Data Analysis Plan (WC# 92441955) for additional details.

6 CHANGES TO PLANNED ANALYSES

Any changes to the planned statistical analyses made prior to performing the analyses will be documented in an amended Statistical Analysis Plan approved prior to performing the analyses. Changes from the planned statistical methods after performing the analyses will be documented in the clinical study report along with a reason for the deviation.

7 PROGRAMMING CONSIDERATIONS

All statistical analyses will be conducted in SAS version 9.3 or higher (SAS Institute, Cary, N.C.)

8 REFERENCES

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