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

INTERRUPT AF - PM009

CLINICAL INVESTIGATION PLAN

Version B

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Sponsored By

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Vendors/Labs	A list of vendors/laboratories involved in the trial is maintained by the sponsor.

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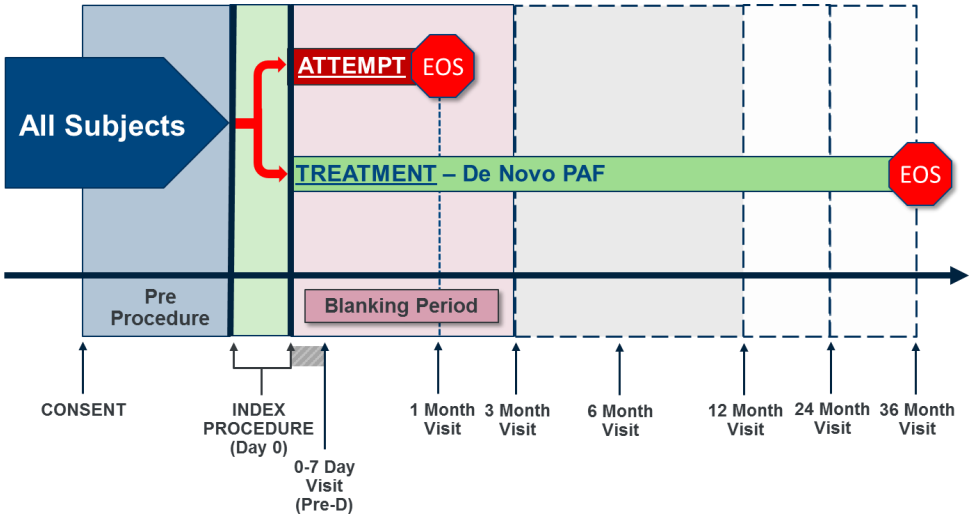
Protocol Section Modified	**Existing Text as Written in Protocol, Version**	**Revised/New Text as Written in Protocol, Version**	**Justification for Modification**
Clinical Contact	Micki Weisman	REMOVED	Update of current clinical contacts.
5.1 Reporting Timelines, Table 2			Dates corrected to reflect due dates based on FDA approval of the initial Protocol
8.5 – Data Requirements	Procedure and fluoroscopy times (first catheter inserted to ablation catheter removed)	Total Procedure times (first catheter inserted to last catheter removed). Total Fluoroscopy Time	Correct Definition of when procedure ends. Separation of Procedure time from Fluoro Time

1. Protocol Synopsis

PROSPECTIVE EVALUATION OF OPEN IRRIGATED ABLATION CATHETERS WITH HIGH RESOLUTION MAPPING TO TREAT PAROXYSMAL ATRIAL FIBRILLATION **INTERRUPT AF**	
Study Objective(s)	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).
Indication(s) for Use	Study devices will be used per approved Indications for Use for each geography.
Devices / System used in the study	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 1or Rhythmia HDx, equipped with Software 1.4 or any successive commercially approved versions. • IntellaMap Orion Catheter
Control Device	There are no control devices in this study

Study Design	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.  **INTERRUPT AF Study Design**
Planned Number of Subjects	The study will enroll 415 subjects.
Planned Number of Sites / Countries	The study is global (US, EU, Asia-Pacific) with 25-50 centers. A minimum of 50% of the sites will be selected from the US. No study site will be allowed to contribute more than 41 subjects (10% of the 415 enrollments requirement).

Primary Safety Endpoint	The primary safety endpoint is defined as the 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 endpoint 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 endpoint 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)

Primary Effectiveness Endpoint	The primary effectiveness endpoint is defined as the event-free rate at 12 months post-procedure.
	
	Primary effectiveness events are defined as:
	• 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, 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

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

Tertiary Endpoint	Chronic effectiveness: Evaluation of 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 withdraw from the study prior to the specified time point without experiencing an event will be censored 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 centers in the study. 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.
Method of Assigning Patients to Treatment	Any subject that signs the consent form, meets eligibility criteria, has any of the specified study devices inserted into the body and successfully completes protocol specific treatment for the intended disease will be assigned to the treatment group.
Follow-up Schedule	Study Follow-ups are at: pre-discharge, 1 month (phone check), 3 months (blanking period), 6 months (phone check), 12 months, 24 months and 36 months.

Data collection overview

Data Collected	ENROLLMENT/ BASELINE	INDEX PROCEDURE (Day 0)	PRE-DISCHARGE (0-7 days post -procedure)	1-MONTH FOLLOW-UP (30±7 days)	3-MONTH FOLLOW-UP (90±30 days)	6-MONTH FOLLOW-UP (180±30 days)	12-MONTH FOLLOW-UP (365± 30 days)	24 MONTH FOLLOW-UP (730 ± 30 days)	36 MONTH FOLLOW-UP (1095 ± 30 days)	ADDITIONAL FOLLOW-UP	REPEAT PROCEDURE
Informed Consent	X										
Inclusion/ Exclusion	X										
Demographic data	X										
Medical History	X										
Vitals	X		X		X		X	X	X	X	
Pre-Procedure Assessment	X										
Imaging	X[a]		X[a]		X[a]		X[a]			X[a]	X[b]
Medication Regimen	X	X	X	X	X	X	X	X	X	X	X
Procedure data		X									X
EQ-5D	X				X	X	X				
AFEQT	X				X	X	X				
12-Lead EKG	X		X		X		X	X	X	X	
Event Monitor					X	X	X			X[c]	
Holter Monitor							X		X		
Documentation of Intervention for AF/AT/AFL				X	X	X	X	X	X	X	
Protocol Deviations	X	X	X	X	X	X	X	X	X	X	X
Adverse Event/Device Deficiency Reporting	X	X	X	X	X	X	X	X	X	X	X

a: If Pulmonary Vein Stenosis suspected or per center standard of care
b: Required for repeat procedures with non-study catheters only
c: If completed before the 12-month follow-up visit

Study Duration	Study is expected to be completed in approximately five years (12-24 month enrollment period with three year follow-up).
Participant Duration	The study duration for each subject is expected to be approximately three years.
Inclusion Criteria	1. History of recurrent symptomatic Paroxysmal Atrial Fibrillation, defined as AFib that terminates spontaneously or with intervention within seven days of onset. Minimum documentation includes a physician's note indicating recurrent self-terminating Atrial Fibrillation AND one electrocardiographically documented AF episode within 6 months prior to enrollment. 2. Subjects who are eligible for an ablation procedure for Paroxysmal Atrial Fibrillation with the Rhythmia Mapping system according to current international and local guidelines 3. Subjects who are eligible for an ablation procedure for Paroxysmal Atrial Fibrillation with a Boston Scientific Open-Irrigated Ablation Catheter according to current international and local guidelines 4. Subjects who are willing and capable of providing informed consent 5. Subjects who are willing and capable of participating in all testing associated with this clinical investigation at an approved clinical investigational center 6. Subjects whose age is 20 years or above, or who are of legal age to give informed consent specific to state and national law.
Exclusion Criteria	1. Subjects enrolled in any other concurrent clinical study, with the exception of local mandatory governmental registries and observational studies/registries, without the written approval from Boston Scientific 2. Subjects unable or unwilling to complete follow-up visits and examination for the duration of the study 3. Subjects who have undergone <u>any</u> previous left atrial cardiac ablation (RF, Cryo, surgical) 4. Subjects who have undergone any cardiac ablation within 30 days prior to enrollment 5. Unrecovered/unresolved Adverse Events from any previous invasive procedure 6. Life expectancy <= three years per physician opinion 7. Women of childbearing potential who are, or plan to become, pregnant during the time of the study (method of assessment upon physician's discretion) 8. Known cardiac thrombus within 60 days prior to enrollment 9. History of CVA, TIA or PE within 90 days prior to enrollment 10. Implanted pacemaker, ICD, or CRT leads within 90 days prior to enrollment 11. Implanted Left atrial appendage closure device prior to the index procedure 12. Prosthetic mitral or tricuspid heart valves (subjects with successful mitral valve repair allowed- annular ring constitutes repair) 13. Left atrial diameter greater than 5.5cm

<table>
<tr><td></td><td>14. Documented or suspected stenosis of any pulmonary veins.
15. Atrial fibrillation secondary to electrolyte imbalance, thyroid disease, or reversible or non-cardiac cause.
16. Contraindication for anticoagulation
17. Clinically significant mitral valve regurgitation or stenosis per investigator discretion.
18. Any cardiac surgery ≤ 90 days from consent date.
19. Any electrocardiographically documented episode of Persistent AFib, defined as AFib lasting longer than 7 days from onset.</td></tr>
<tr><td colspan="2">Statistical Methods</td></tr>
<tr><td>Primary Statistical Hypotheses and Statistical Test Methods</td><td>
<table>
<tr><th>Endpoint</th><th>Hypothesis</th><th>Analysis Method</th></tr>
<tr><td>Primary Safety Endpoint</td><td>The primary safety endpoint event-free rate at 12 months post-procedure >85%</td><td>Kaplan-Meier rate with pointwise log-log confidence limit</td></tr>
<tr><td>Primary Effectiveness Endpoint</td><td>The primary effectiveness event-free rate at 12 months post-procedure >50%</td><td>Kaplan-Meier rate with pointwise log-log confidence limit</td></tr>
<tr><td>Secondary Effectiveness Endpoint</td><td>The secondary effectiveness event-free rate at 12 months post-procedure >50%</td><td>Kaplan-Meier rate with pointwise log-log confidence limit</td></tr>
</table>
</td></tr>
<tr><td>Sample Size Parameters</td><td>The sample size for the study is driven by the primary safety endpoint which requires a minimum sample size of 329 TREATMENT subjects. 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:
<table>
<tr><th>Assumptions</th><th>Primary Safety</th></tr>
<tr><td>Expected rate</td><td>90%</td></tr>
<tr><td>Performance goal</td><td>85%</td></tr>
<tr><td>Attrition (per year)</td><td>7.5%</td></tr>
<tr><td>Significance level (one-sided)</td><td>5%</td></tr>
<tr><td>Power</td><td>80%</td></tr>
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</td></tr>
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2. Introduction

2.1. *Background*

Atrial fibrillation (AF) is the most common sustained arrhythmia, affecting approximately 2.5 million people in North America, 4.5 million people in Europe and estimated to affect a total of 33.5 million people worldwide[1-4]. The prevalence and incidence of AF are increasing over time due to the aging of the population and a substantial increase in the age-specific occurrence of AF[3-5].

Mortality risk is 1.5 to 2-fold greater for AF patients after accounting for other factors, with AF accounting for approximately 15 percent of all strokes in the US[2,6]. In addition, atrial fibrillation significantly impairs quality of life, with up to two-thirds of patients reporting that it is disruptive to their lives[7,8].

Paroxysmal Atrial Fibrillation (PAF) is defined as atrial fibrillation which terminates spontaneously or with intervention within seven days of onset; this AF type comprises between 25% and 62% of cases[2,9]. Patients with PAF may exhibit symptoms including palpitations, shortness of breath, syncope, fatigue, and lightheadedness, and have serious adverse effects such as hemodynamic compromise, embolic stroke, myocardial ischemia or infarction. However, PAF may also present without symptoms while it retains the same risk of thrombus formation with embolic potential[10].

Treatment options for AF include medical management, cardioversion, implantable devices, surgery, and ablation therapy to eliminate the arrhythmia[2,3,11]. The approach to therapy for AF has evolved due to an altered view of the pathophysiology of this condition. While previous models of treatment focused on the importance of multiple re-entrant wavelets throughout the atria to sustain the arrhythmia, it has been increasingly recognized that focal pulmonary vein triggers can account for 80 to 95 percent of paroxysmal AF cases that are drug resistant. The principal objective of AF ablation is the electrical disconnection of the pulmonary vein triggers from the atrial substrate which is referred to as pulmonary vein isolation (PVI). To achieve this clinical effect, ablation is performed around the pulmonary vein (PV) orifice on the PV antrum[12-16].

Several technologies have been developed to date to support PVI ablation with radiofrequency (RF) ablation, including the Open Irrigated cooling method, currently available among different single point ablation catheters [17-19]. Open Irrigated catheters have important advantages in RF ablation, as surface cooling during energy delivery reduces heating at the point of highest current density where excessive temperatures would normally produce charring, crater formation and impedance rises. Thus, higher levels of energy can be delivered safely using cooled tip ablation with more reliable delivery of radiofrequency current to the tissue[18].

The introduction of three-dimensional electro-anatomical mapping systems (EMS) also represented an important development in contemporary cardiac electrophysiology[20]. Electro-anatomical mapping systems are widely used in PVI to facilitate ablation by integrating

functional and anatomical information allowing substrate characterization and individual ablation strategies, and also facilitating the tracking of intracardiac electrodes and the navigation of catheters during PVI[21]. More recently ultra-high resolution EMS are also specifically used to better characterize and confirm isolation of the pulmonary veins [22].

2.2. *Study Rationale*

The Rhythmia Mapping System's ability to produce high density maps enables for gap detection that is critical for de novo PAF procedures. Utilizing a Rhythmia map-based validation workflow targets the gaps that inherently lead to recurrence following de novo PAF ablation. This study aims to demonstrate the efficacy of this Rhythmia map-based workflow by evaluating acute and long-term safety and effectiveness outcomes.

In December 2017, the Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) approved a new indication for the Boston Scientific Blazer Open-Irrigated Ablation Catheter and IntellaNav Open-Irrigated Ablation Catheter to include treatment of drug refractory, recurrent, symptomatic, paroxysmal atrial fibrillation (P150005/S014). This post-approval study (PAS) has been designed to comply with the request of providing continued reasonable assurance of the safety and effectiveness of the approved device, by evaluating the short (peri-procedural and one-year) and longer-term (through three years) safety and effectiveness of the Boston Scientific Open-Irrigated catheters for de novo atrial fibrillation ablation procedures.

In addition, Boston Scientific has added to this PAS protocol the IntellaTip MiFi Open-Irrigated Ablation Catheter and IntellaNav MiFi Open-Irrigated Ablation Catheter under review for P150005/S035 for the expanded indication of PAF that is identical to the indication of P150005/S014.

3. Device Description

3.1. *Open-Irrigated Ablation Catheters*

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

- Blazer Open-Irrigated Ablation Catheter (Blazer OI)
- IntellaNav Open-Irrigated Ablation Catheter (IntellaNav OI)
- IntellaNav MiFi Open-Irrigated Ablation Catheter (IntellaNav MiFi OI)
- IntellaTip MiFi Open-Irrigated Ablation Catheter (IntellaTip MiFi OI)

The BSC Open-Irrigated catheters are designed to deliver RF energy to catheter tip electrode for cardiac ablation. The BSC OI catheters incorporate an open-irrigated cooling mechanism through a tip that is partitioned into two chambers. The proximal chamber circulates normal saline (0.9 %) within the tip to cool the proximal electrode and mitigate overheating while the distal chamber allows the fluid to flow through six irrigation holes into the patient's vasculature, thereby cooling the tip/tissue interface. A luer connection at the proximal end of

the handle connects the catheter to an Irrigation Tubing Set, allowing an Irrigation Pump to generate the flow of saline to the catheter.

The electrode segment of the catheters is comprised of a tip electrode and three ring electrodes. The tip electrode of all the BSC OI catheters has an embedded temperature sensor and delivers RF energy for cardiac ablation. Additionally, the IntellaTip MiFi OI and the IntellaNav MiFi OI include three mini-electrodes in the catheter tip to provide high-resolution electrograms (EGM) and the IntellaNav OI and the IntellaNav MiFi OI catheters include a position sensor for magnetic tracking and navigation of the catheter on a Rhythmia Mapping System. The ring electrodes record EGM signals for mapping and deliver stimulus for pacing. The catheters interface with standard RF generators through the Rhythmia Connection Box. The catheter handle includes the electrical connector for the cable connection to the Connection Box and one luer fitting used to connect the catheter to the Irrigation Tubing Set.

3.2. *Rhythmia Mapping System*

The Rhythmia™ Mapping System, the Rhythmia HDx Mapping System, and the IntellaMap Orion™ mapping catheter are designed for electroanatomical mapping in catheter ablation procedures. The Rhythmia Mapping System tracks catheters inside the heart in order to visualize their location and construct geometric shells. The Rhythmia Mapping System is also capable of using intra-cardiac location and electrical information to display electroanatomical maps - electrical activity information on the constructed geometry. Such electrical information can be visualized in 3D and in color. The commercially available system operates the latest commercially-available software (version 1.4 or newer). Rhythmia HDx equipped with software version 2.0 may include the DirectSense feature. This feature allows for an impedance-based metric that can be used in conjunction with other clinical diagnostic measures (e.g., electrogram amplitude, fluoroscopy, intracardiac echocardiography, magnetic and impedance navigation, and tactile feedback) to inform catheter stability and navigation within the heart.

Subsequent versions of the Rhythmia Mapping System (including but not limited to the already commercially released upgrade, the Rhythmia HDx) and software may be used during this study as they become commercially available after regulatory approval in their geography.

3.3. *IntellaMap Orion High Resolution Mapping Catheter*

The IntellaMap Orion High Resolution Mapping Catheter is an 8.5F, 115 cm working length, 64-electrode steerable catheter. The basket-shaped distal region consists of eight splines that comprise the electrode array. The proximal end has a handle that extends to a cable with a connector. The handle includes bi-directional articulation controls and a deployment slider that activates the electrode array into a basket shape once inside the heart. A flushing port extends from the back of the connector for connection to a continuous pressurized saline drip. The catheter is supplied with an 8.5F insertion sleeve for insertion through the hemostasis valve of an introducer sheath. A sensor in the catheter tip enables the position of the distal region of the catheter to be tracked in space when used with the Rhythmia™ Mapping System. Subsequent versions of the IntellaMap Orion mapping catheter may be used during this study as they become commercially available after regulatory approval in their geography.

4. Study Objectives and Endpoints

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

The primary objective of the study is to assess acute and long-term outcomes for the Rhythmia Mapping System in conjunction with Boston Scientific Open-Irrigated Ablation Catheters to treat Paroxysmal Atrial Fibrillation for de novo cases. In addition, the study serves to comply with the FDA request of a PAS for the Blazer OI, IntellaNav OI, IntellaTip MiFi OI, and IntellaNav MiFi OI Ablation catheters.

4.1. *Primary Safety Endpoint*

The primary safety endpoint is defined as the 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 endpoint 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 endpoint 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)

Table 1: Primary Safety Endpoint Definitions

Term	Definition
Atrio-Esophageal Fistula	A connection between the atrium and the lumen of the esophagus

Table 1: Primary Safety Endpoint Definitions

Term	Definition
AV block	A conduction disturbance that results in the partial inability of an electrical impulse generated in the atria to reach the ventricles.
Cardiac tamponade/ Perforation	The development of a significant pericardial effusion during or within 30 days of undergoing an AF ablation procedure. A significant pericardial effusion is one that results in hemodynamic compromise, requires elective or urgent pericardiocentesis, or results in a 1-cm or more pericardial effusion as documented by echocardiography. [27]
Myocardial infarction (in the context of AF ablation)	The presence of any one of the following criteria: (1) detection of ECG changes indicative of new ischemia (new STT wave changes or new LBBB) that persist for more than 1 hour; (2) development of new pathological Q waves on an ECG; (3) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. [27]
Pericardial Effusion	A collection of fluid or blood in the pericardial space around the heart or in pleural space around the lungs. [27]
Pericarditis	Inflammation of the pericardium surrounding the heart. Pericarditis should be considered a major complication following ablation if it results in an effusion that leads to hemodynamic compromise or requires pericardiocentesis, prolongs hospitalization by more than 48 hours, requires hospitalization, or persists for more than 30 days following the ablation procedure. [27]
Pneumothorax	Collapse of the lung due to an abrupt change in the intrapleural pressure within the chest cavity.
Pulmonary edema/heart failure	Ineffective pumping of the heart leading to an accumulation of fluid in the lungs. Typical symptoms include shortness of breath with exertion, difficulty breathing when lying flat and leg or ankle swelling.
Pulmonary Vein Stenosis (Significant)	Pulmonary vein stenosis is defined as a reduction of the diameter of a PV or PV branch. For the primary safety endpoint of this study, significant pulmonary vein stenosis is defined as symptomatic and requiring intervention.
Stroke/Cerebrovascular accident (CVA)	Rapid onset of a focal or global neurological deficit with at least one of the following: change in level of consciousness, hemiplegia, hemiparesis, numbness or sensory loss affecting one side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke. Duration of a focal or global neurological deficit ≥24 hours; OR <24 hours if therapeutic intervention(s) were performed (e.g., thrombolytic therapy or intracranial angioplasty); OR available neuroimaging documents a new hemorrhage or infarct; OR the neurological deficit results in death. No other readily identifiable non-stroke cause for the clinical presentation (e.g., brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences). Confirmation of the diagnosis by at least one of the following: neurology or neurosurgical specialist; neuroimaging procedure (MRI or CT scan or cerebral angiography); lumbar puncture (i.e., spinal fluid analysis diagnostic of intracranial hemorrhage) [27]
Thromboembolism	The blockage of a blood vessel lumen by air or solid material such as device fragments, blood clot or other tissues that have migrated from another anatomic site.

Table 1: Primary Safety Endpoint Definitions

Term	Definition
Transient Ischemic Attack (TIA)	New focal neurological deficit with rapid symptom resolution (usually 1 to 2 hours), always within 24 hours; neuroimaging without tissue injury. [27]
Vagal Nerve Injury/Gastroparesis	Vagal nerve injury is defined as injury to the vagal nerve that results in esophageal dysmotility or gastroparesis. Vagal nerve injury is considered to be a major complication if it prolongs hospitalization, requires hospitalization, or results in ongoing symptoms for more than 30 days following an ablation procedure. [27]
Vascular access complications	Development of a hematoma, an AV fistula, or a pseudoaneurysm. A major vascular complication is defined as one that requires intervention, such as surgical repair or transfusion, prolongs the hospital stay, or requires hospital admission. [27]

4.2. *Primary Effectiveness Endpoint*

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

Primary effectiveness events are defined as:

- 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, 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

4.3. *Secondary Effectiveness Endpoint*

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

4.4. *Tertiary Endpoints*

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 withdraw from the study prior to the specified time point without experiencing an event will be censored 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.

5. Study Design

The INTERRUPT AF study is a global, prospective, non-randomized, multicenter study. The study will serve as the Post Approval Study for the Blazer OI, IntellaNav OI, IntellaTip MiFi OI, and IntellaNav MiFi OI Ablation catheters. All study devices will be used per instruction as they become commercially available after regulatory approval in their geography. Therefore, the index procedure for the INTERRUPT AF study is the same procedure that a subject would undergo if they were not participating in this study.

For the purposes of the study, De Novo is defined as subjects undergoing first ablation procedure for PAF with no prior left atrium ablations (RF, Cryo, Surgical).

5.1. *Scale and Duration*

A total of 415 subjects will be included in the study to ensure a minimum of 329 TREATMENT subjects.

The study is global and will include 25-50 sites in the United States, Europe and Asia-Pacific. A minimum of 50% of the sites will be selected from the United States.

To reduce the impact of individual center bias, no study site will be allowed to contribute more than 41 subjects (10% of the 415 enrollments requirement).

Each subject will be followed at specified time points after the ablation procedure (index procedure) with a follow-up duration of three years. A study subject's participation will be considered complete when all protocol required visits have been completed as indicated in Figure 5.2-1.

Accordingly, the study is expected to be completed in approximately five years (two-year enrollment period with three-year follow-up.

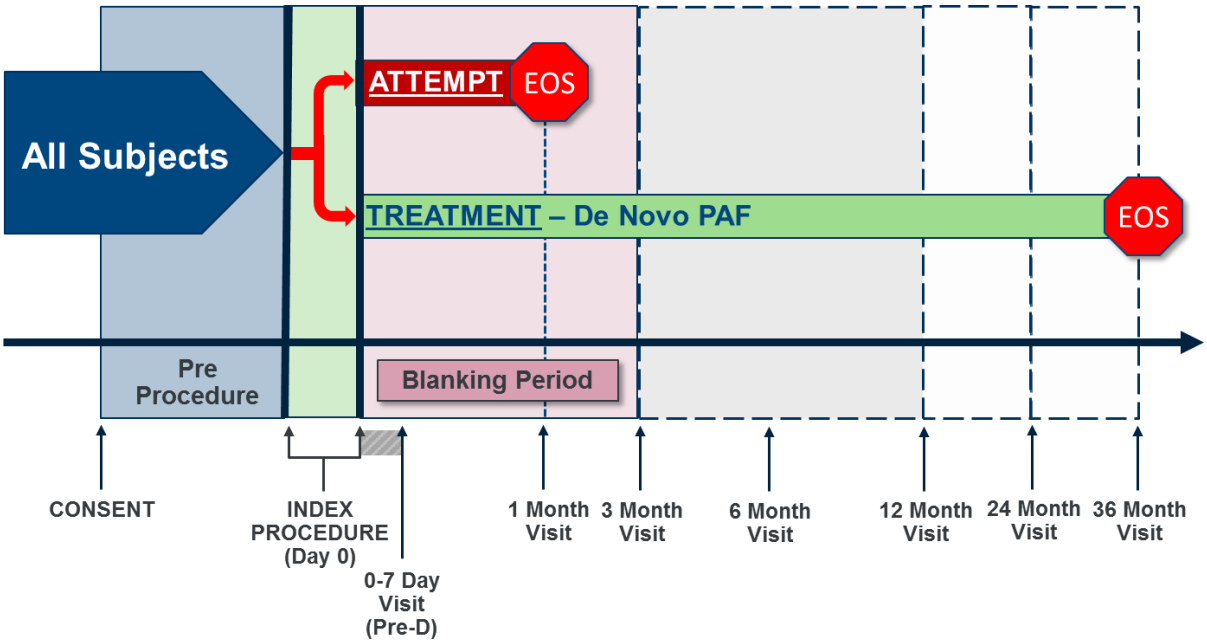

Figure 5.1-1: INTERRUPT AF Study Design

Table 2: INTERRUPT AF Study Timeline	
Milestone	**Forecast Date**
Start	Upon FDA approval of PAS Protocol
First Enrollment	Approximately 120 days after FDA approval of the protocol
Enrollment Plan	Given the global prevalence of Paroxysmal Atrial Fibrillation, it is estimated that each activated site can each enroll 1 subject per month. It is anticipated that it will take 12-24 months to enroll the 415 subjects.
Progress Updates	Progress reports will be provided every six months for the first two years from the date of FDA Approval of PAS Protocol, then annually thereafter. Section 9.3.1 contains details of the progress report content.
Primary Objective Analysis	Within 3 months of 12-Month Visit Completion for all subjects.
Final Post Approval Study Report	Within 3 months of 36-Month Visit Completion for all subjects.

Anticipated Reporting Dates	Assuming FDA Approval of PAS Protocol on 01NOV2018, First Patient In on 01APR2019 and 18-month enrollment period: • 6 Month Interim PAS Status Report (~01MAY2019) • 12 Month Interim PAS Status Report (~01NOV2019) • 18 Month Interim PAS Status Report (~01MAY2020) • 24 Month Interim PAS Status Report (~01NOV2020) • 36 Month Interim PAS Status Report (~01NOV2021) • 48 Month Interim PAS Status Report (~01NOV2022) • Primary Objective Analysis (~01DEC2021)* • Final Post Approval Study Report (~01DEC2023) * The Primary Objective Analysis will be provided within 3 months of all 12 Month visits being completed in a Primary Endpoint Report. If the timing of the Primary Endpoint Report aligns with a scheduled interim report, the two will be combined.

5.2. *Treatment Assignment*

All subjects who meet the eligibility criteria as per Sections 6.2 and 6.3 and sign the informed consent will be considered enrolled. Subjects will be classified based on patient status classification as per Section 7.3.

5.3. *Justification for the Study Design*

This post-market study aims to collect acute and long-term data for the Rhythmia Mapping System and Boston Scientific OI Catheters for de novo PAF ablation.

The Blazer OI, IntellaNav OI, IntellaTip MiFi OI, and IntellaNav MiFi OI Ablation Catheters have been approved by FDA for ablation treatment of PAF. The present study serves to comply with the request of providing continued reasonable assurance of the safety and effectiveness of the approved devices in a de novo PAF population. Any of the BSC Open Irrigated study catheters listed in Section 3.1 are allowed for use in the study once they are commercially available after regulatory approval in their geography for PAF Ablation.

6. Subject Selection

6.1. *Study Population and Eligibility*

Subjects included in the INTERRUPT AF study should be selected from the investigator's general patient population indicated for catheter ablation of PAF. Investigators are responsible for screening all potential subjects and selecting those who meet the eligibility criteria for the study as described in Sections 6.2 and 6.3 below.

6.2. *Inclusion Criteria*

Subjects who meet all of the following criteria (see Table 3) may be given consideration for inclusion in this clinical investigation, provided no exclusion criterion (see Section 6.3) is met.

Table 3: Inclusion Criteria

Inclusion Criteria	1. History of recurrent symptomatic Paroxysmal Atrial Fibrillation, defined as AFib that terminates spontaneously or with intervention within seven days of onset. Minimum documentation includes a physician's note indicating recurrent self-terminating Atrial Fibrillation AND one electrocardiographically documented AF episode within 6 months prior to enrollment. 2. Subjects who are eligible for an ablation procedure for Paroxysmal Atrial Fibrillation with the Rhythmia Mapping system according to current international and local guidelines; 3. Subjects who are eligible for an ablation procedure for Paroxysmal Atrial Fibrillation with a BSC Open-Irrigated Ablation Catheter according to current international and local guidelines; 4. Subjects who are willing and capable of providing informed consent; 5. Subjects who are willing and capable of participating in all testing associated with this clinical investigation at an approved clinical investigational center; 6. Subjects whose age is 20 years or above, or who are of legal age to give informed consent specific to state and national law.

6.3. *Exclusion Criteria*

Subjects who meet any one of the following criteria (Table 4) will be excluded from this clinical study.

Table 4: Exclusion Criteria

Exclusion Criteria	1. Subjects enrolled in any other concurrent clinical study, with the exception of local mandatory governmental registries and observational studies/registries, without the written approval from Boston Scientific 2. Subjects unable or unwilling to complete follow-up visits and examination for the duration of the study; 3. Subjects who have undergone <u>any</u> previous left atrial cardiac ablation (RF, Cryo, surgical) 4. Subjects who have undergone any cardiac ablation within 30 days prior to enrollment; 5. Unrecovered/unresolved Adverse Events from any previous invasive procedure; 6. Life expectancy <= three years per physician opinion 7. Women of childbearing potential who are, or plan to become, pregnant during the time of the study (method of assessment upon physician's discretion) 8. Known cardiac thrombus within 60 days prior to enrollment 9. History of CVA, TIA or PE within 90 days prior to enrollment 10. Implanted pacemaker, ICD, or CRT leads within 90 days prior to enrollment 11. Implanted Left atrial appendage closure device prior to index procedure 12. Prosthetic mitral or tricuspid heart valves (subjects with successful mitral valve repair allowed- annular ring constitutes repair) 13. Left atrial diameter greater than 5.5cm 14. Documented or suspected stenosis of any pulmonary veins. 15. Atrial fibrillation secondary to electrolyte imbalance, thyroid disease, or reversible or non-cardiac cause. 16. Contraindication for anticoagulation 17. Clinically significant mitral valve regurgitation or stenosis per investigator discretion. 18. Any cardiac surgery ≤ 90 days from consent date. 19. Any electrocardiographically documented episode of Persistent AFib, defined as AFib lasting longer than 7 days from onset.

7. Subject Accountability

7.1. *Point of Enrollment*

Investigators will select subjects who are appropriate for study inclusion as per eligibility criteria (Section 6.2 and 6.3). Subjects who meet all eligibility criteria and have signed and dated the Informed Consent Form are considered enrolled in the study. All subject enrollments will be counted against the enrollment ceiling for the study.

7.2. *Withdrawal*

All subjects enrolled in the clinical study (including those withdrawn from the clinical study) shall be accounted for and documented. If a subject withdraws from the INTERRUPT AF study, the reason(s) shall be reported.

Reasons for withdrawal may include physician discretion, change in inclusion/exclusion status, subject choice to withdraw consent, lost to follow-up, or death. While study withdrawal is discouraged, subjects may withdraw from the study at any time, with or without reason, and without prejudice to further treatment. All applicable electronic case report forms (eCRFs) up to the point of subject withdrawal and an "End of Study" eCRF must be completed. For subjects who are "lost to follow-up" the investigator/center should have at least three documented attempts to contact the subject prior to completion of the "End of Study" eCRF. No additional data may be collected after a subject has been withdrawn from the study or withdraws his/her consent, for whatever reason. All open adverse events should be closed or documented as chronic. Data collected up to the point of subject withdrawal may be used. If such withdrawal is due to problems related to device safety or performance, the investigator shall ask for the subject's permission to follow his/her status/condition.

7.3. *Subject Status and Classification*

All enrolled subjects will be classified into one of three categories based on their progress and completion of key events. Classification will determine how data gathered from them will be stored and evaluated.

- **INTENT**: Any subject that signs the consent form but does not have any study devices inserted into the body. Subjects who are enrolled in the study but do not undergo ablation procedure within 60 days from consent signature date may not be reconsented and will be withdrawn from the study and classified as "INTENT". INTENT subjects will count towards the enrollment ceiling and will not be used for analysis of the endpoints. INTENT subjects will not be followed for any additional visits after withdrawal. For these subjects an "End of Study" form must be completed. The original signed Informed Consent must be maintained in the center's subject file.
- **ATTEMPT**: Any subject that signs the consent form, meets eligibility criteria and has any protocol defined study device inserted into the body but does not receive RF ablation per protocol. Additionally, any subject not treated with a BSC OI Catheter **and** the Rhythmia System will be considered an ATTEMPT. Use of the IntellaMap Orion Catheter is required but will not affect subject classification. Procedures that do not utilize the IntellaMap Orion Catheter will have a protocol deviation entered. Subjects will be followed for one month for safety reporting only. Therefore, ATTEMPT subjects will not be assigned an event monitor for study purposes. All applicable case report forms must be completed, including Baseline, data pertaining to the Index

procedure, Adverse Event reporting and one-month follow-up. ATTEMPT subjects will count towards the enrollment ceiling and will not be used for analyses of the primary endpoint. The original signed Informed Consent must be maintained in the center's study file.

- **TREATMENT**: Any subject that signs the consent form, meets eligibility criteria and has the specified study devices inserted into the body and undergoes protocol specific treatment for the intended disease.

7.4. *End-of-Study Definition*

A subject enrolled in INTERRUPT AF is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last applicable procedure shown in the Data Collection Schedule (table 8.1-1).

8. Study Methods

8.1. *Data Collection*

The data collection schedule is shown in Table 5.

Table 5: Data Collection Schedule

Data Collected	**ENROLLMENT/ BASELINE**	**INDEX PROCEDURE** (Day 0)	**PRE-DISCHARGE** (0-7 days post -procedure)	**1-MONTH FOLLOW-UP** (30±7 days)	**3-MONTH FOLLOW-UP** (90±30 days)	**6-MONTH FOLLOW-UP** (180±30 days)	**12-MONTH FOLLOW-UP** (365± 30 days)	**24 MONTH FOLLOW-UP** (730 ± 30 days)	**36 MONTH FOLLOW-UP** (1095 ± 30 days)	**ADDITIONAL FOLLOW-UP**	**REPEAT PROCEDURE**
Informed Consent	X										
Inclusion/Exclusion	X										
Demographic data	X										
Medical History	X										
Vitals	X		X		X		X	X	X	X	
Pre-Procedure Assessment	X										
Imaging	X[a]		X[a]		X[a]		X[a]			X[a]	X[b]
Medication Regimen	X	X	X	X	X	X	X	X	X	X	X
Procedure data		X									X
EQ-5D	X				X	X	X				
AFEQT	X				X	X	X				
12-Lead EKG	X		X		X		X	X	X	X	
Event Monitor					X	X	X			X[c]	
Holter Monitor							X		X		
Documentation of Intervention for AF/AT/AFL				X	X	X	X	X	X	X	
Protocol Deviations	X	X	X	X	X	X	X	X	X	X	X
Adverse Event/Device Deficiency Reporting	X	X	X	X	X	X	X	X	X	X	X

a: If Pulmonary Vein Stenosis suspected or per center standard of care
b: Required for repeat procedures with non-study catheters only
c: If completed before the 12-month follow-up visit

8.2. *Study Candidate Screening*

Investigators are responsible for screening all subjects and selecting those who are appropriate for study inclusion. The subjects selected for participation should be from the investigator's general patient population. The investigator is expected to follow standard of care testing to diagnose and screen subjects for inclusion in the study.

8.3. *Informed Consent*

Patients who meet all of the inclusion criteria and none of the exclusion criteria and agree to participate in the INTERRUPT AF study must provide written informed consent approved by the regional regulatory body and the investigational center's IRB/EC prior to study participation and study specific testing or data collection.

The subject should be given ample time to consider participation and ask questions if necessary. An approved informed consent form (ICF) shall be signed and personally dated by the subject (or legal representative). The original, signed document is to be kept with the subject's file and a copy of the signed ICF must be provided to the subject. The index procedure must be performed within 60 days post ICF signature. In case the index procedure has not been performed within this time period, the subject may not be reconsented and will be classified as an INTENT (see section 8.3).

For additional information regarding the informed consent process, refer to Section 19.

8.4. *Enrollment/Baseline Visit*

Subjects who provide written consent and meet all of the study enrollment criteria are enrolled in the study.

Enrolled subjects will have baseline data collected. The data collection at baseline includes:

- Visit date;
- Demographic data, including: age at time of consent, gender, race and ethnicity;
- Vitals including: height, weight, resting heart rate, systolic and diastolic blood pressure;
- Medical history, including:
    - Underlying cardiovascular disease, if any;
    - Prior history of cardiac events including: acute myocardial infarction, CVA, TIA, PE or transient ischemic attack;
    - Prior surgical interventions and/or cardiac procedures including: PTCA, CABG, pacemaker implantation, ICD implant, CRT implant, cardiac valve interventions, left atrial appendage closure, patent foramen ovale intervention, heart transplant or procedures for implantation of other intracardiac devices;
    - Detailed history of all arrhythmias and previous cardiac ablation procedures (catheter delivered or surgically performed), if any, including date of latest ablation procedure and any concomitant procedures (e.g., valve surgery, left atrial appendage closure or ligation, etc.), treated arrhythmia(s) and outcome;
    - Non-cardiac comorbidities.

- Pre-procedure assessment of Left Ventricular Ejection Fraction, Left Ventricular Diastolic Diameter, and Left Atrial Diameter within the past six months including data collection methods (if available)
- Current cardiovascular medication regimen including anti arrhythmic, anticoagulation and antiplatelet agents.
- Imaging
- 12-Lead EKG data including ongoing rhythm
- Quality of Life Instruments (AFEQT and EQ-5D-5L)

Evidence of PAF in the medical history should be documented and reported in the CRFs including date of last recorded episode, source of recording (Holter, EKG, etc) and treatment history (drug, cardioversion, etc).

8.4.1. **Medications**

8.4.2. **Anti-Arrhythmic Drugs**

It is recommended that all Anti-Arrhythmic Drugs (AADs) should be stopped at least five half-lives before the procedure; amiodarone should be stopped one month before the procedure.

It is recommended that AADs only be prescribed after the procedure if a subject has a documented arrhythmia recurrence. Post-procedure AADs are allowed per physician's discretion but new AADs should not be prescribed unless considered medically necessary. At eight weeks, investigators should remove subjects from AADs to appropriately assess the subject for early arrhythmia recurrence that may require a repeat ablation procedure within the blanking period (on or before day 90)

If the investigator determines that the subject must remain on an AAD after the blanking period, the subject will be considered a Primary Effectiveness Failure.

Treatment with Class II/IV medications for conditions other than control of arrhythmia recurrence is also permitted and will be documented. Every effort should be made to keep those drugs at a stable dose over the entire course of the study.

8.4.3. **Anticoagulation**

It is expected that the patient population for the study will have differing anticoagulation therapies. The requirements outlined below represent the minimum requirement of the study. Additional screening/testing is allowed if deemed necessary by the investigator.

The following subject groups should get a trans-esophageal echocardiogram (TEE) or equivalent to confirm absence of thrombus in the left atrium within 48 hours prior to the ablation:

- Patient presenting in Atrial Fibrillation at the time of the index procedure
- Patients presenting in Sinus Rhythm but with unknown anticoagulation pre-procedure

- Patient presenting in Atrial Fibrillation that have not been therapeutically anticoagulated for three weeks
- Patients with known cardiac thrombus within the past 90 days

It is also recommended that the following groups get a trans-esophageal echocardiogram (TEE) or equivalent to confirm absence of thrombus in the left atrium within 48 hours prior to the ablation:

- Patient presenting in Atrial Fibrillation and that have been therapeutically anticoagulated for three weeks
- Patient presenting in Sinus Rhythm that have not been therapeutically anticoagulated for three weeks

Confirming the absence of thrombus is not required for subjects in sinus rhythm that have therapeutic anticoagulation for three weeks.

Administration of anticoagulation on the morning of the index procedure is optional and investigators are encouraged to follow their standard of care. Per the Instructions For Use of the study devices, the activated coagulation/clotting time (ACT) level must be brought to a level ≥300 seconds and be checked at clinically appropriate intervals per center's SOC. No ablation can be performed until a minimum ACT of 300 seconds is obtained.

After the index procedure, all subjects will be required to be anticoagulated, using the drug determined best for the subject by the investigator, for a minimum of 60 days. All anticoagulation medications and INR levels, if applicable, will be collected throughout the course of the study.

8.5. *Ablation (index) procedure*

The index procedure for the INTERRUPT AF Study will consist of de novo PAF procedures. For the purposes of this protocol, de novo procedures are defined as AF procedures in which there has been no prior ablation in the Left Atrium (LA).

Esophageal temperature monitoring is highly recommended and should be performed per the center's standard of care. Esophageal temperature should be monitored and ablation delivery should be guided by rapid temperature rise or when temperature reaches a predefined threshold per standard of care.

The objective of the procedure is map-based electrical isolation of all pulmonary veins. Physicians will follow their preferred ablation workflow utilizing a Boston Scientific Open-Irrigated Catheter following all applicable Instructions for Use.

Once isolation of PVs has been attempted, the investigator may check for gaps with a validation map (vMap). This may be done on a per vein, per side, or whole chamber basis according the investigator's discretion. vMaps must be created while the subject is in sinus rhythm or during pacing. Adenosine or isoproterenol testing may be performed per center's standard of care and will be noted in the CRF.

Final confirmation of entrance block must be by vMap made at least 20 minutes after the last ablation (for that PV). Exit block verification is also highly recommended and will be noted in the CRF if completed.

Electrical isolation of the veins must be demonstrated by the absence of electrical propagation within the ablation lines.

Additional ablations may be performed according to medical judgement and clinical practice. If gaps are present, additional RF applications can be applied as required. Ablation of Induced Arrhythmias is allowed during the procedure as well as any previously documented arrhythmias. All additional ablations will be noted on the CRF.

Mapping/Ablation data collected during the procedure will include but may not be limited to:

Data Requirements
Catheter model(s) and lot/serial number(s) used
Presenting Rhythm
Esophageal Temperature Monitoring (if applicable)
Programmed ablation catheter fluid infusion rates
Location of all previous ablations in any chamber (RF, Cryo, Surgical)
Primary ablation targets
Location of and reason for additional ablations performed beyond PVI
Detection of gaps in ablation lines of index procedure (including locations)
Number of ablation attempts (See Table 11 for definition) needed to close gap in ablation line/per gap for index procedure
Did PV isolation terminate AF? What rhythm did AF terminate to?
Adenosine testing result (if performed)
Isoproterenol testing information (if performed)
Was isolation achieved for each PV at the end of the procedure? (Documented via electrogram printouts)
Name of map(s) that demonstrates PVI
Acute success verification technique
Was exit block tested? If, so was exit block achieved?
Total Procedure Time (first catheter inserted to last catheter removed)
Total Fluoroscopy Time
Total RF time for the procedure
Total fluid infused from ablation catheter
Total mapping time
Number of maps created
Mapping time for each map
Reason for map creation (list for each map)
Map Completeness
Number of points in each map
Specific use of Rhythmia features
Rhythm at end of case
Was Cardioversion performed during the procedure? If so, when?
Electronic Map Data*

* At the conclusion of the procedure, the Electronic Map Data collected through the Rhythmia Mapping System will be saved and stored in anonymized form by the site or sponsor representative onto external media provided by the Sponsor. Media will be returned to the Sponsor at the end of the study or at periodic intervals during the study.

8.6. *Pre-Discharge Follow-up*

The pre-discharge follow-up visit should be completed before the subject is discharged from the hospital. The visit should occur within seven days post-index procedure. If the subject is to remain in the hospital beyond seven days post-index procedure, then the pre-discharge follow-up visit should be conducted before the eighth day.

The data collection at Pre-Discharge includes:

- Date of visit;
- Vitals including: height, weight, resting heart rate, systolic and diastolic blood pressure
- Rhythm at time of visit (12-Lead EKG);
- Variations in current medication regimen
- Imaging (collected only if performed, if PV Stenosis suspected or according to center's practice)
- Reportable Adverse Events, if applicable
- Protocol Deviations, if applicable

8.7. *One-Month Follow-up (Phone Check)*

The one-month follow-up should be completed between 23 and 37 days post-procedure. The one-month follow-up can be performed over the phone or in clinic according to the site's standard practice.

The data collection at the one-month follow-up includes:

- Date of visit
- Review of any symptomatic transmissions (event monitor)
- Variations in current medication regimen
- Documentation of any intervention for AF/AT/AFL (e.g.: Repeat Procedure, Cardioversion), if applicable
- Reportable Adverse Events, if applicable
- Protocol Deviations, if applicable

8.8. *Three-Month Follow-up*

The three-month follow-up visit should be completed between 60 and 120 days post-procedure. Due to the range for the visit completion and the endpoint requirement for medication, AAD medication changes made during the three-month follow-up visit will be counted as being made within the blanking period, but efforts should be made to remove subjects from AADs by eight weeks post-procedure to allow for complete washout.

The data collection at the three-month follow-up visit includes:

- Date of visit
- Vitals including: height, weight, resting heart rate, systolic and diastolic blood pressure
- Rhythm at time of visit (12-Lead EKG)
- Review of any available symptomatic or asymptomatic transmissions (event monitor)
- Variations in current medication regimen
- Imaging (collected only if performed, if PV Stenosis suspected or according to center's practice)
- Quality of Life Instruments (AFEQT and EQ-5D-5L)
- Documentation of any intervention for AF/AT/AFL (e.g.: Repeat Procedure, Cardioversion), if applicable
- Reportable Adverse Events, if applicable
- Protocol Deviations, if applicable

8.9. *Six-Month Follow-up (Phone Check)*

The six-month follow-up should be completed between 150 and 210 days post-procedure. The six-month follow-up can be performed over the phone or in clinic according to the site's standard practice.

The data collection at the six-month follow-up includes:

- Date of visit
- Review of any symptomatic or asymptomatic transmissions (event monitor)
- Variations in current medication regimen
- Imaging (collected only if performed, if PV Stenosis suspected or according to center's practice)
- Quality of Life Instruments (AFEQT and EQ-5D-5L)
- Documentation of any intervention for AF/AT/AFL (e.g.: Repeat Procedure, Cardioversion), if applicable
- Reportable Adverse Events, if applicable
- Protocol Deviations, if applicable

8.10. *12-Month Follow-up*

The 12-month follow-up visit should be completed between 335 and 395 days post-procedure.

The data collection at the 12-month follow-up visit includes:

- Date of visit
- Vitals including: height, weight, resting heart rate, systolic and diastolic blood pressure
- Rhythm at time of visit (12-Lead EKG);

- Review of any symptomatic or asymptomatic transmissions (event monitor);
- Collection and Review of 24-hour Holter Monitor for symptomatic or asymptomatic events
- Variations in current medication regimen;
- Imaging (collected only if performed, if PV Stenosis suspected or according to center's practice)
- Quality of Life Instruments (AFEQT and EQ-5D-5L)
- Documentation of any intervention for AF/AT/AFL (e.g.: Repeat Procedure, Cardioversion), if applicable
- Reportable Adverse Events, if applicable
- Protocol Deviations, if applicable

8.11. *24-Month Follow-up*

The 24-month follow-up visit should be completed between 700 and 760 days post-procedure.

The data collection at the 24-month follow-up visit includes:

- Date of visit
- Vitals including: height, weight, resting heart rate, systolic and diastolic blood pressure
- Rhythm at time of visit (12-Lead EKG)
- Variations in current medication regimen
- Documentation of any intervention for AF/AT/AFL (e.g.: Repeat Procedure, Cardioversion), if applicable
- Reportable Adverse Events, if applicable
- Protocol Deviations, if applicable

8.12. *36 Month Follow-up*

36-month follow-up visit should be completed between 1065 and 1125 days post-procedure.

The data collection at the 36-month follow-up visit includes:

- Date of visit
- Vitals including: height, weight, resting heart rate, systolic and diastolic blood pressure
- Rhythm at time of visit (12-Lead EKG)
- Collection and Review of 24-hour Holter Monitor for symptomatic or asymptomatic events
- Variations in current medication regimen
- Documentation of any intervention for AF/AT/AFL (e.g.: Repeat Procedure, Cardioversion), if applicable
- Reportable Adverse Events, if applicable
- Protocol Deviations, if applicable

8.13. *Additional Follow-up Visits*

An Additional follow-up visit is any subject visit triggered by subject symptoms that is not already defined as one of the study visits.

If subjects experience symptoms associated with cardiac arrhythmias (e.g. palpitations, lightheadedness, syncope, dyspnea) during the first 12 months, they will be instructed to record the arrhythmia on the event monitor. The investigator will review the information transmitted and will contact the subject to schedule an additional office visit if necessary.

In addition to determining the best course of action for the subject (repeat ablation, medication adjustment), during the visit, the following will be collected:

- Date
- Vitals including: height, weight, resting heart rate, systolic and diastolic blood pressure
- Rhythm at time of visit (12-Lead EKG)
- Variations in current medication regimen
- Imaging (collected only if performed, if PV Stenosis suspected or according to center's practice)
- If performed before the 12-month visit, review of symptomatic episode event monitor transmissions by the subject since the last follow-up
- Any intervention for AF/AT/AFL (e.g.: Repeat Procedure, Cardioversion)
- Reportable Adverse Events, if applicable
- Protocol Deviations, if applicable

8.14. *Repeat Ablation Procedure*

It is known that a repeat ablation procedure may be necessary in certain subjects after the index ablation procedure due to recurrences of PAF or other tachyarrhythmias requiring treatment. One repeat procedure is allowed within the blanking period if considered medically necessary due to subject's intolerability of the arrhythmia. Data collection requirements for the repeat procedure are the same as those for the index procedure.

If an investigator believes it is in the subject's best interest to perform the ablation with a non-study catheter, the investigator may choose to withdraw the subject from the study prior to performing the procedure. Prior to study withdrawal and undergoing the repeat procedure with a different (non-study) catheter, imaging of the PVs is required. The appropriate type of imaging performed may be determined by the investigator. As available, the PV images must be reviewed against the pre-ablation imaging from the index procedure to rule out PV stenosis from the index ablation procedure. In addition, repeat ablation with a non-study catheter must occur ≥30 days after the previous ablation procedure.

8.15. *Study Completion*

Active data collection for each subject will be complete after subjects complete the 36-month follow-up visit (including Holter Monitor). Sites will need to complete the "End of Study" CRF to signify study completion.

8.16. *Source Documents*

It is preferable that original source documents are maintained, when available. In lieu of original source documents, certified copies are required to be maintained. A certified copy is a copy (irrespective of the type of media used) of the original record that has been verified (i.e., by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original. Source documentation includes but is not limited to those items noted in Table 6.

Table 6: Source Documentation Requirements

Requirement	Disposition
Informed consent documentation process	Retain at Center
Medical history documents pertaining to eligibility criteria	Retain at Center
Documentation of demographics data	Retain at Center
Vitals	Retain at Center
Medication Changes	Retain at Center
Medical history	Retain at Center
Quality of Life Instruments (AFEQT and EQ-5D-5L)	Retain in subject binder
Imaging	Retain at Center
12-Lead EKGs data including ongoing rhythm	Retain at Center
Imaging, per standard of care	Retain at Center
Recording System Print-Outs, showing entrance block for each Pulmonary Vein	Retain in subject binder
Recording lab logs, showing the time of entrance block (20 minutes after last ablation)	Retain in subject binder
Signed Technical Source Form	Retain in subject binder
Adverse Events	Retain at Center
In the event of a subject death: • Death narrative • Relevant medical records • Death Certificate • Autopsy report	Submit one copy to BSC, Retain one copy at center

Additional source documentation may be required upon request of BSC.

9. Statistical Considerations

9.1. *Endpoints*

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.

9.1.1. **Primary Safety Endpoint**

The primary safety endpoint 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)

9.1.1.1. 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 $\leq 85\%$[24, 25]

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

9.1.1.2. 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.

9.1.1.3. 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.

9.1.2. **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

9.1.2.1. 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_o: 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%

9.1.2.2. 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.

9.1.2.3. Statistical Methods

For the primary effectiveness endpoint, the Kaplan-Meier 12 month (365-day) primary effectiveness event-free rate will be calculated. Subjects who 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 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.

9.1.3. **Secondary Effectiveness Endpoint**

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

Secondary 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 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 Class II/IV medications taken for control of AF/AT/AFL recurrence

9.1.3.1. 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%

9.1.3.2. 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.

9.1.3.3. Statistical Methods

For the secondary effectiveness endpoint, the Kaplan-Meier 12 month (365-day) secondary effectiveness event-free rate will be calculated. Subjects who 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 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.

9.1.4. **Tertiary Endpoint**

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

- Recurrence 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 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 withdraw from the study prior to the specified time point without experiencing an event will be censored 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 centers in the study. 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.

9.1.5. **Total sample size**

A total of 415 subjects will be enrolled in the study to ensure a minimum of 329 TREATMENT subjects.

9.2. *General Statistical Methods*

9.2.1. **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.

9.2.2. **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.

9.2.3. **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%.

9.2.4. **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 minimum 415 enrollment total).

9.3. *Data Analyses*

9.3.1. **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).

9.3.2. 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**.**

9.3.3. 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.

9.3.4. 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.

9.3.5. **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)

9.3.6. **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.

10. Data Management

10.1. *Data Collection, Processing, and Review*

Subject data will be recorded in a limited access secure electronic data capture (EDC) system.

The clinical database will reside on a production server hosted by Medidata EDC System. All changes made to the clinical data will be captured in an electronic audit trail and available for review by the sponsor or its representative. The associated Rave software and database have been designed to meet regulatory compliance for deployment as part of a validated system compliant with laws and regulations applicable to the conduct of clinical studies pertaining to the use of electronic records and signatures. Database backups are performed regularly.

The Investigator provides his/her electronic signature on the appropriate electronic case report forms (eCRFs) in compliance with local regulations. A written signature on printouts of the eCRFs must also be provided if required by local regulation. Changes to data previously submitted to the sponsor require a new electronic signature by the Investigator acknowledging and approving the changes.

Visual and/or electronic data review will be performed to identify possible data discrepancies. Manual and/or automatic queries will be created in the Medidata EDC system and will be issued to the site for appropriate response. Site staff will be responsible for resolving all queries in the database.

10.2. *Data Retention*

The Principal Investigator or his/her designee or Investigational site will maintain all essential study documents and source documentation that support the data collected on the study subjects in compliance with applicable regulatory requirements.

The Principal Investigator or his/her designee will take measures to prevent accidental or premature destruction of these documents. If for any reason the Principal Investigator or his/her designee withdraws responsibility for maintaining these essential documents, custody must be transferred to an individual who will assume responsibility and BSC must receive written notification of this custodial change. Sites are required to inform Boston Scientific in writing where paper or electronic files are maintained in case files are stored off site and are not readily available.

10.3. *Technical Source Forms*

The Technical Source Form (TSF) is the approved document to capture protocol required data elements that are not duplicated in any other source documents. This form requires review and approval by the investigator and is to be used by the study sites as a source document.

Collection and completion of all information on the Technical Source Form is the responsibility of the appropriately delegated site personnel. If available, the mapping specialist will provide the delegated site personnel with the study related data collected during the case directly from the Rhythmia Mapping system.

At the conclusion of the procedure, the completed technical source form must be signed (and initialed as needed) by the following people:

- the Delegated Site Personnel completing the forms
- the Delegated Investigator conducting and/or supervising the case
- the Rhythmia Mapping Specialist supporting the case

10.4. *Core Laboratories*

10.4.1. **Event Monitor and 24-Hour Holter Monitors**

10.4.1.1. Event Monitor

A centralized research company will provide the center and/or subject all necessary instructions and/or materials related to the use of the event monitor. Only TREATMENT subjects will be provided with an event monitor, such as a Trans-Telephonic Monitor (TTM), either prior to discharge from the hospital or will be sent to the subject's residence immediately following discharge. Subjects will be instructed to collect any symptomatic ECG recordings with the event monitor and transmit the recordings to the centralized research company. All events will be analyzed by the centralized research company to determine if the episodes are associated with arrhythmia recurrence.

Within the first 90 days (3 months) after the index ablation procedure (blanking period), TREATMENT subjects will be instructed to transmit all symptomatic episodes for detection and treatment of early recurrences. All subjects will be instructed to submit at least two

transmissions every month from their 3 month follow-up visit until their 12 month follow-up visit to ensure continued symptomatic reporting compliance. If a subject has a symptomatic episode within the month, that transmission will count towards the required transmissions. The centralized research company will work with the investigational site and directly with the subject to ensure reporting compliance.

All event monitors must be returned to the centralized research company upon completion of a subject's 12-month follow-up or withdrawal from the study.

10.4.1.2. 24-Hour Holter Monitors

All TREATMENT subjects will be provided with 24-Hour Holter Monitors during the 12-month and 36-month follow-up visit window.

Investigational centers will be trained on the set-up of the monitors and will provide the subjects with the instructions necessary to complete the test. If a subject has a symptomatic episode while wearing the Holter Monitor, they will be strongly encouraged to report the symptoms to their physician. Once the Holter Monitor is returned to the centralized research company, the monitor will be analyzed for all symptomatic and asymptomatic arrhythmia episodes, and investigators will be informed of the results.

11. Deviations

An Investigator must not make any changes or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency. An investigator shall notify the sponsor and the reviewing IRB/EC/REB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency, and those deviations which affect the scientific integrity of the clinical investigation. Such notice shall be given as soon as possible, but no later than five working days after the emergency occurred, or per prevailing local requirements, if sooner than five working days.

All deviations from the investigational plan, with the reason for the deviation and the date of occurrence, must be documented and reported to the sponsor using EDC. Sites may also be required to report deviations to the IRB/EC/REB, per local guidelines and government regulations.

Deviations will be reviewed and evaluated on an ongoing basis and, as necessary, appropriate corrective and preventive actions (including IRB/EC/REB/FDA notification, site re-training, or site discontinuation/termination) will be put into place by the sponsor.

12. Compliance

12.1. *Statement of Compliance*

This study will be conducted in accordance with post market clinical follow-up guidelines and will follow the applicable sections of ISO 14155 (Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice), the relevant parts of the ICH Guidelines for Good Clinical Practices, ethical principles that have their origins in the Declaration of Helsinki,

and applicable individual country laws and regulations. The study shall not begin until the required approval/favorable opinion from the IRB/EC/REB and/or regulatory authority has been obtained, if appropriate. Also, the study shall not begin prior to issuance of the site Authorization to Enroll, as provided by the sponsor. Any additional requirements imposed by the IRB/EC/REB or regulatory authority shall be followed, if appropriate.

12.2. *Investigator Responsibilities*

The Principal Investigator of an investigational site is responsible for ensuring that the study is conducted in accordance with the Clinical Study Agreement, the clinical investigation plan, the spirit of ISO 14155, ethical principles that have their origins in the Declaration of Helsinki, any conditions of approval imposed by the reviewing IRB/EC/REB, and prevailing local and/or country laws and/or regulations, whichever affords the greater protection to the subject.

The Principal Investigator's responsibilities include, but are not limited to, the following.

- Prior to beginning the study, sign the Clinical Study Agreement and comply with the Investigator responsibilities as described in such Agreement.
- Provide his/her qualifications and experience to assume responsibility for the proper conduct of the study and that of key members of the site team through up-to-date curriculum vitae or other relevant documentation and disclose potential conflicts of interest, including financial, that may interfere with the conduct of the clinical study or interpretation of results.
- Make no changes in or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency; document and explain any deviation from the approved protocol that occurred during the course of the clinical investigation.
- Create and maintain source documents throughout the clinical study and ensure their availability with direct access during monitoring visits or audits; ensure that all clinical-investigation-related records are retained per requirements.
- Ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.
- Record, report, and assess (seriousness and relationship to the device/procedure) every adverse event as applicable per the protocol and observed device deficiency.
- Report to sponsor, per the protocol requirements, all SAEs and device deficiencies that could have led to a SADE and potential/USADE or UADE.
- Report to the IRB/EC/REB and regulatory authorities any SAEs and device deficiencies that could have led to a SADE and potential/USADE or UADE, if required by applicable laws or regulations or this protocol or by the IRB/EC/REB, and supply BSC with any additional requested information related to the safety reporting of a particular event.
- Allow the sponsor to perform monitoring and auditing activities, and be accessible to the clinical research monitor or auditor and respond to questions during monitoring visits or audit(s).
- Allow and support regulatory authorities and the IRB/EC/REB when performing auditing activities.

- Ensure that informed consent is obtained in accordance with applicable laws, this protocol and local IRB/EC/REB requirements.
- Provide adequate medical care to a subject during and after a subject's participation in a clinical study in the case of adverse events, as described in the Informed Consent Form (ICF).
- Inform the subject of the nature and possible cause of any adverse events experienced.
- As applicable, provide the subject with necessary instructions on proper use, handling, storage, and return of the device when it is used/operated by the subject.
- Inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required.
- Provide the subject with well-defined procedures for possible emergency situations related to the clinical study, and make the necessary arrangements for emergency treatment, including decoding procedures for blinded/masked clinical investigations, as needed.
- Ensure that clinical medical records are clearly marked to indicate that the subject is enrolled in this clinical study.
- Ensure that, if appropriate, subjects enrolled in the clinical investigation are provided with some means of showing their participation in the clinical investigation, together with identification and compliance information for concomitant treatment measures (contact address and telephone numbers shall be provided).
- Inform, with the subject's approval or when required by national regulations, the subject's personal physician about the subject's participation in the clinical investigation.
- Make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from clinical investigation while fully respecting the subject's rights.
- Ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation.

12.2.1. **Delegation of Responsibility**

When specific tasks are delegated by an investigator, including but not limited to conducting the informed consent process, the Principal Investigator is responsible for providing appropriate training, ensuring delegates are competent to perform the tasks they have been delegated and adequate supervision of those to whom tasks are delegated. Where there is a sub-Investigator at a site, the sub-Investigator should not be delegated the primary supervisory responsibility for the site. The Principal Investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

12.3. *Institutional Review Board/ Ethics Committee*

The investigational site will obtain the written and dated approval/favorable opinion of the IRB/EC/REB for the clinical investigation before recruiting subjects and implementing all subsequent amendments, if required.

A copy of the written IRB/EC/REB and/or competent authority (CA) approval of the protocol (or permission to conduct the study) and Informed Consent Form, must be received by the sponsor before recruitment of subjects into the study. Prior approval must also be obtained for other materials related to subject recruitment or which will be provided to the subject.

Any amendment to the protocol will require review and approval by the IRB/EC/REB before the changes are implemented to the study. All changes to the ICF will be IRB/EC/REB approved; a determination will be made regarding whether a new ICF needs to be obtained from participants who provided consent, using a previously approved ICF.

Annual IRB/EC/REB approval and renewals will be obtained throughout the duration of the study as required by applicable local/country laws or regulations or IRB/EC/REB requirements. Copies of the study reports and the IRB/EC/REB continuance of approval must be provided to the sponsor.

12.4. *Sponsor Responsibilities*

All information and data sent to BSC concerning subjects or their participation in this study will be considered confidential by BSC and will be kept confidential in accordance with all applicable laws and regulations. Only authorized BSC personnel and/or a BSC representative including, but not limited to Contract Research Organization (CRO), will have access to this information. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this study. Study data collected during this study may be used by BSC for the purposes of this study, publication, and to support future research and/or other business purposes, such as overseeing and improving the performance of its device, new medical research and proposals for developing new medical products and procedures. All data used in the analysis and reporting of this study or shared with a third-party researcher will be without identifiable reference to specific subjects.

Information received during the study will not be used to market to subjects; subject names will not be placed on any mailing lists or sold to anyone for marketing purposes.

12.4.1. **Role of Boston Scientific Representatives**

Boston Scientific personnel can provide technical support to the investigator and other health care personnel (collectively HCP) as needed during index procedure, testing required by the protocol, and follow-ups. Support may include HCP training, addressing HCP questions, or providing clarifications to HCPs concerning the operation of BSC equipment/devices.

At the request of the investigator and while under investigator supervision, typical tasks of BSC personnel may include the following as allowed by local regulations:

- Setting up, calibrating and/or operating parameters to investigator-requested settings of the Rhythmia™ Mapping System and other supporting equipment during the preparation and execution of the mapping and ablation procedure.
- Clarifying device behavior, operation or diagnostic output as requested by the investigator or other health care personnel.
- Interaction with Boston Scientific noninvasive equipment (Rhythmia workstation and accessories) and interpretation of information contained therein to support the collection

of required information by the delegated site staff. BSC Personnel may review for completeness and accuracy.

- Collect/Archive anonymized data directly from the Rhythmia Mapping System or other supporting equipment**,** print reports and/or provide any original documentation to the clinical site as source.
- Interact with the subject to accomplish requested activities.
- Assist with the conduct of testing specified in the protocol.
- Observe any testing or medical procedures to provide information relevant to protocol compliance.

Boston Scientific personnel will not do the following.

- Practice medicine
- Provide medical diagnosis or treatment to subjects
- Discuss a subject's condition or treatment with a subject without the approval and presence of the investigator
- Record data on Source documents
- Independently collect critical study data (defined as primary or secondary endpoint data)
- Enter data in electronic data capture systems or on paper case report forms

12.5. *Insurance*

Where required by local/country regulation, proof and type of insurance coverage, by BSC for subjects in the study will be obtained.

13.Monitoring

Monitoring will be performed by Boston Scientific or its designees during the study. A combination of on-site, remote, or central monitoring will be used to assess continued compliance with the protocol and applicable regulations. This includes ensuring proper informed consent process, review of safety data, and adherence to protocol defined visit schedule. In addition, the clinical research monitor verifies that study records are adequately maintained, that data are reported in a satisfactory manner with respect to timeliness, adequacy, and accuracy, and that the Principal Investigator continues to have sufficient staff and IRB approved facilities to conduct the study safely and effectively. The Principal Investigator/institution guarantees direct access to original source documents by BSC personnel, their designees, and appropriate regulatory authorities.

The study may also be subject to a quality assurance audit by BSC or its designees, as well as inspection by appropriate regulatory authorities. It is important that the Principal Investigator and relevant study personnel are available during on-site monitoring visits or audits and that sufficient time is devoted to the process.

14.Potential Risks and Benefits

14.1. *Directions for Use*

Please refer to the Directions for Use for an overview of anticipated adverse (device) effects, and risks associated to the commercial device(s).

14.2. *Risks associated with Participation in the Clinical Study*

Risks associated with participation in the study are those applicable to paroxysmal RF ablation and mapping procedures.

14.3. *Risk Minimization Actions*

Additional risks may exist. Risks can be minimized through compliance with this protocol, performing procedures in the appropriate hospital environment, adherence to subject selection criteria, close monitoring of the subject's physiologic status during research procedures and/or follow-ups and by promptly supplying BSC with all pertinent information required by this protocol.

14.4. *Anticipated Benefits*

There may be no benefit to the subject. However, currently enrolled subjects may benefit from their participation in this study due to a closer follow up. Medical science and future patients may benefit from the results of this clinical protocol.

14.5. *Risk to Benefit Rationale, if applicable*

Risk management activities, including Hazard Analyses (HA) and Failure Mode Effects Analyses (FMEA), have been performed on the Blazer OI catheters and cables (used with Stockert 70/EP-Shuttle Generator/Cool Flow Pump system) to identify and analyze known and foreseeable hazards (in both normal and fault conditions) and reasonably foreseeable sequences or combinations of events that could result from using this product and the risks associated with each hazard. Mitigations have been implemented in the design, processes, and/or labeling and Directions For Use of the product to reduce the residual risk of each hazard as necessary and practicable. The HA has been reviewed and approved and the remaining risks are acceptable when weighed against the intended benefits to the subject.

15.Safety Reporting

15.1. *Reportable Events by investigational site to Boston Scientific*

It is the responsibility of the investigator to assess and report to BSC any event which occurs in any of following categories:

- 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.

When possible, the medical diagnosis should be reported as the Event Term instead of individual symptoms. If it is unclear whether or not an event fits one of the above categories, or if the event cannot be isolated from the device or procedure, it should be submitted as an adverse event and/or device deficiency.

All Events related to the study device or study procedure must be reported as *Adverse Events*. Pre-existing conditions and pre-planned hospitalizations at time of enrollment (including AFib, AFl, ATach) are not considered *Adverse Events*, however if they meet the criteria for *Serious Adverse Events*, they should be reported as an SAE. As stated in Table 7, all medical interventions are considered *Serious Adverse Events*, however medical intervention due to arrhythmia recurrence is only considered a *Serious Adverse Event* if the intervention takes place after the 90-day Blanking Period.

Death should not be reported as an *Serious Adverse Event*, but should only be reflected as an outcome of one (1) specific SAE (see Table 7 for AE definitions).

The following definitions will be used for defining in-patient or prolonged hospitalizations for SAE classification purposes:

- In-patient hospitalizations will be defined as ≥24 hours in duration or <24 hours with medical intravenous therapy or surgical intervention
- Prolonged hospitalization will be defined as ≥72 hours after the index procedure for reasons other than anticoagulation

Refer to Directions for Use for the known risks associated with the commercial device(s).

15.2. *Definitions and Classification*

Adverse event definitions are provided in Table 7. Administrative edits were made on the safety definitions from ISO 14155 and MEDDEV 2.7/3 for clarification purposes.

Table 7: Safety Definitions

Term	Definition
Adverse Event (AE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, whether or not related to the study medical device. **NOTE 1**: This includes events related to the study medical device or comparator. **NOTE 2**: This definition includes events related to the procedures involved.

Table 7: Safety Definitions

Term	Definition
	NOTE 3: For users or other persons, this definition is restricted to events related to the study medical device.
Adverse Device Effect (ADE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Adverse event related to the use of the study medical device **NOTE 1**: This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the study medical device. **NOTE 2**: This definition includes any event resulting from use error or intentional abnormal use of the study medical device.
Serious Adverse Event (SAE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Note: This definition meets the reporting objectives and requirements of ISO 14155 and MEDDEV 2.7/3. Adverse event that: a) Led to death, b) Led to serious deterioration in the health of the subject as defined by either: 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, or 3) in-patient hospitalization or prolongation of existing hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function c) Led to fetal distress, fetal death, or a congenital abnormality or birth defect. **NOTE 1:** Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without a serious deterioration in health, is not considered a serious adverse event.
Serious Adverse Device Effect (SADE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated Adverse Device Effect (UADE) *Ref: 21 CFR Part 812*	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.
Unanticipated Serious Adverse Device Effect (USADE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report. **NOTE 1**: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

Table 7: Safety Definitions

Term	Definition
Device Deficiency *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	An inadequacy of the study medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer.

15.3. *Relationship to Device(s)*

The Investigator must assess the relationship of the reportable AE to the device, or procedure. See criteria in Table 8:

Table 8: Criteria for Assessing Relationship of Study Device or Procedure to Adverse Event

Classification	Description
Not Related *Ref: MEDDEV 2.7/3*	Relationship to the device or procedures can be excluded when: - the event is not a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has no temporal relationship with the use of the study device or the procedures; - the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; - the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event; - the event involves a body-site or an organ not expected to be affected by the device or procedure; - the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors); - the event does not depend on a false result given by the study device used for diagnosis, when applicable; harms to the subject are not clearly due to use error; - In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.
Unlikely Related *Ref: MEDDEV 2.7/3*	The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
Possibly Related *Ref: MEDDEV 2.7/3*	The relationship with the use of the study device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.
Probably Related *Ref: MEDDEV 2.7/3*	The relationship with the use of the study device seems relevant and/or the event cannot be reasonably explained by another cause, but additional information may be obtained.

Table 8: Criteria for Assessing Relationship of Study Device or Procedure to Adverse Event

Classification	Description
Causal Relationship *Ref: MEDDEV 2.7/3*	The serious event is associated with the study device or with procedures beyond reasonable doubt when: - the event is a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has a temporal relationship with the study device use/application or procedures; - the event involves a body-site or organ that -the study device or procedures are applied to; -the study device or procedures have an effect on; - the serious event follows a known response pattern to the medical device (if the response pattern is previously known); - the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible); - other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; - harm to the subject is due to error in use; - the event depends on a false result given by the study device used for diagnosis, when applicable; - In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

15.4. *Investigator Reporting Requirements*

The communication requirements for reporting to BSC are as shown in Table 9.

Adverse events and device deficiencies must always be reported through the eCRF system. However, in the event that an alternative method of reporting is necessary (i.e. the eCRF system is unavailable), please report the adverse event or device deficiency to Boston Scientific by sending the Event Notification Form via email to the following email address:

INTERRUPTAF.Safety@bsci.com

Table 9: Event Communication Requirements

Event Classification	**Communication Method**	**Communication Timeline post-market studies*** (MEDDEV 2.12/2: GUIDELINES ON A MEDICAL DEVICE VIGILANCE SYSTEM)
Unanticipated Adverse Device Effect / Unanticipated Serious Adverse Device Effect	Complete AE eCRF page with all available new and updated information.	• Within one business day of first becoming aware of the event. • Terminating at the end of the study.
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• Upon BSC request.
Serious Adverse Event	Complete AE eCRF page with all available new and updated information.	• Within 10 business days after becoming aware of the event or as per local/regional regulations. • All Death Events must be reported within 3 calendar days • For Austria: within two business days of first becoming aware of the event. • Reporting required through End of Study.
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• Upon BSC request.
Serious Adverse Device Effects	Complete AE eCRF page with all available new and updated information.	• Within two business days of first becoming aware of the event or as per local/regional regulations. • Reporting required through End of Study.
	Provide all relevant source documentation (unidentified) for reported event.	• Upon BSC request.

Event Classification	Communication Method	Communication Timeline post-market studies* (MEDDEV 2.12/2: GUIDELINES ON A MEDICAL DEVICE VIGILANCE SYSTEM)
Device Deficiencies (including but not limited to failures, malfunctions, and product nonconformities) Note: Any Device Deficiency that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable event.	Complete Device Deficiency CRF with all available new and updated information.	• Within two business days of first becoming aware of the event. Reporting required through End of Study.
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• At request of sponsor
Adverse Event including Adverse Device Effects	Complete AE eCRF page, which contains such information as date of AE, treatment of AE resolution, assessment of seriousness and relationship to the device.	• In a timely manner (e.g. recommend within 30 business days) after becoming aware of the information • Reporting required through End of Study.
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	

15.5. *Boston Scientific Device Deficiencies*

All device deficiencies (including but not limited to failure, malfunction, use errors, product non-conformities, labeling errors and inadequacy in the information associated with the study devices) will be documented and reported to BSC. If possible, the device(s) should be returned to BSC for analysis. Instructions for returning the device(s) will be provided upon request. If it is not possible to return the device, the investigator should document why the device was not returned and the final disposition of the device. Device deficiencies should also be documented in the subject's source records.

Device deficiencies are not adverse events. However, an adverse event that results from a device deficiency would be recorded as an adverse event on the appropriate eCRF in addition to completing a Device Deficiency CRF.

15.6. *Reporting to Regulatory Authorities / IRBs / ECs / REBs/ Investigators*

BSC is responsible for reporting adverse event information to all participating Principal Investigators, IRBs/ECs/REBs and regulatory authorities, as applicable.

The Principal Investigator is responsible for informing the IRB/EC/REB, and regulatory authorities of UADEs and SAEs as required by local/regional regulations.

15.7. *Subject Death Reporting*

A subject death during the study should be reported to Boston Scientific as soon as possible and, in any event, within three (3) calendar days of site notification. The site's IRB/EC must be notified of any deaths in accordance with that site's IRB/EC policies and procedures.

Notification of death must include a detailed narrative (death letter) that provides detailed information describing the circumstances surrounding the death. A death narrative in the local language is acceptable, if accompanied by a translation in English. The details listed below should be addressed in the death narrative, in order for BSC to understand the circumstance surrounding the death:

- Date and time of death;
- Place death occurred;
- Immediate cause of death;
- Rhythm at the time of death, if known (include any available documentation);
- Whether the death was related to the study devices, clinical investigation, procedure, or subject condition;
- Whether or not the death was witnessed;
- Whether the subject had worsening heart failure;
- Any other circumstances surrounding the death;
- Approximate time interval from the initiating event to death (temporal course) – items to consider include, but are not limited to: information regarding last time subject was seen by investigator, last office visit, etc.
- Investigator or co-Investigator signature and date.

Also submit the following documentation, upon request from sponsor:

If the subject expired in the hospital:

- A copy of the medical records for that admission (e.g., H&P, consults, test results, operative reports, and/or progress notes from the hospital chart);
- Death certificate (if available);
- Autopsy report (if applicable);
- If the subject expired outside of the hospital (e.g., home):
- A copy of the most recent clinic visit (if not already submitted to Boston Scientific);
- Death certificate (if available);
- If applicable, the Boston Scientific catheters should be returned promptly to Boston Scientific CRM/EP for analysis.

16. Informed Consent

Subject participation in this clinical study is voluntary. Informed Consent is required from each subject or his/her legally authorized representative. The Investigator is responsible for ensuring that Informed Consent is obtained prior to the use of any study devices, study-required procedures and/or testing, or data collection.

The obtaining and documentation of Informed Consent must be in accordance with the principles of the Declaration of Helsinki, ISO 14155, any applicable national regulations, and local Ethics Committee and/or Regulatory authority, as applicable. The ICF must be accepted by BSC or its delegate (e.g. CRO), and approved by the site's IRB/EC/REB, or central IRB, if applicable.

Boston Scientific will provide a study-specific template of the ICF to investigators participating in this study. The ICF template may be modified to meet the requirements of the investigative site's IRB/EC/REB. Any modification requires acceptance from BSC prior to use of the form. The ICF must be in a language understandable to the subject and if needed, BSC will assist the site in obtaining a written consent translation. Translated consent forms must also have IRB/EC/REB approval prior to their use. Privacy language shall be included in the body of the form or as a separate form as applicable.

The process of obtaining Informed Consent shall at a minimum include the following steps, as well as any other steps required by applicable laws, rules, regulations and guidelines:

- be conducted by the Principal Investigator or designee authorized to conduct the process,
- include a description of all aspects of the clinical study that are relevant to the subject's decision to participate throughout the clinical study,
- avoid any coercion of or undue influence of subjects to participate,
- not waive or appear to waive subject's legal rights,
- use native language that is non-technical and understandable to the subject or his/her legal representative,
- provide ample time for the subject to consider participation and ask questions if necessary,
- ensure important new information is provided to new and existing subjects throughout the clinical study.

The ICF shall always be signed and personally dated by the subject or legal representative competent to sign the ICF under the applicable laws, rules, regulations and guidelines and by the investigator and/or an authorized designee responsible for conducting the informed consent process. If a legal representative signs, the subject shall be asked to provide informed consent for continued participation as soon as his/her medical condition allows. The original signed ICF will be retained by the site and a copy of the signed and dated document and any other written information must be given to the person signing the form.

Failure to obtain subject consent will be reported by BSC to the applicable regulatory authority according to their requirements (e.g., FDA requirement is within five working days of learning of such an event). Any violations of the informed consent process must be reported as deviations to the sponsor and local regulatory authorities (e.g. IRB/EC/REB), as appropriate.

If new information becomes available that can significantly affect a subject's future health and medical care, that information shall be provided to the affected subject(s) in written form via a revised ICF or, in some situations, enrolled subjects may be requested to sign and date an addendum to the ICF. In addition to new significant information during the course of a study, other situations may necessitate revision of the ICF, such as if there are amendments to the applicable laws, protocol, a change in Principal Investigator, administrative changes, or following annual review by the IRB/EC/REB. The new version of the ICF must be approved by the IRB/EC/REB. Acceptance by Boston Scientific is required if changes to the revised ICF are requested by the site's IRB/EC/REB. The IRB/EC/REB will determine the subject population to be re-consented.

17. Committees

17.1. *Safety Monitoring Process*

Clinical Sites will report all study device related AEs, study procedure related AEs, and serious AEs to the sponsor as assessed by the clinical investigator. Investigators will be tasked to determine whether a subject has experienced one of the events specified in Section 4.1, counting towards the primary safety endpoint.

Since device and procedure relatedness do not affect the study endpoints, an independent CEC is not necessary to eliminate bias. The determination of relatedness is used for BSC safety assessment, but not in determining endpoint events. NOTE: The primary safety endpoint includes all deaths within 7 days or pre-discharge (whichever is later) regardless of relatedness to study device or procedure.

All reported adverse events will be reviewed on a regular basis by BSC's Medical Safety Group and study team to evaluate subject safety. The BSC Medical Safety group includes physicians with expertise in Electrophysiology and with the necessary therapeutic and subject matter expertise to evaluate and classify the events. During scheduled monitoring activities, clinical research monitors will support this continuous review through their review of source document and other data information.

17.2. *Steering Committee*

A Steering Committee composed of the sponsor's Clinical Management, the study Principal Investigator, and other prominent Electrophysiologists from around the globe has been convened for this study. Responsibilities for the Committee may include oversight of the overall conduct of the study with regard to protocol development, study progress, subject safety, overall data quality and integrity, and first line review and final decision making of independent medical reviewer recommendations, as well as disseminating any study results through appropriate scientific sessions and publications. Steering Committee members may participate in the review and approval of all requests for data analysis, abstract and manuscript preparation, and submission.

18.Suspension or Termination

18.1. *Premature Termination of the Study*

Boston Scientific reserves the right to terminate the study at any stage but intends to exercise this right only for valid scientific or business reasons and reasons related to protection of subjects. Investigators, associated IRBs/ECs/REBs, and regulatory authorities, as applicable, will be notified in writing in the event of study termination.

18.2. *Criteria for Premature Termination of the Study*

Possible reasons for premature study termination include, but are not limited to, the following.

- The occurrence of unanticipated adverse device effects that present a significant or unreasonable risk to subjects enrolled in the study.
- An enrollment rate far below expectation that prejudices the conclusion of the study.
- A decision on the part of Boston Scientific to suspend or discontinue development/marketing of the device.

18.3. *Termination of Study Participation by the Investigator or Withdrawal of IRB/ EC/REB Approval*

Any investigator, or associated IRB/ EC/ REB or regulatory authority in the INTERRUPT AF Study may discontinue participation in the study or withdraw approval of the study, respectively, with suitable written notice to Boston Scientific. Investigators, associated IRBs/ECs/REBs, and regulatory authorities, as applicable, will be notified in writing in the event of these occurrences.

18.4. *Requirements for Documentation and Subject Follow-up*

In the event of premature study termination, a written statement as to why the premature termination has occurred will be provided to all participating sites by Boston Scientific. The IRB/EC/REB and regulatory authorities, as applicable, will be notified. Detailed information on how enrolled subjects will be managed thereafter will be provided.

In the event an IRB/EC/REB terminates participation in the study, participating investigators, associated IRBs/ECs/REBs, and regulatory authorities, as applicable, will be notified in writing. Detailed information on how enrolled subjects will be managed thereafter will be provided by Boston Scientific.

In the event a Principal Investigator terminates participation in the study, study responsibility will be transferred to another investigator, if possible. In the event there are no opportunities to transfer Principal Investigator responsibility; detailed information on how enrolled subjects will be managed thereafter will be provided by Boston Scientific.

The Principal Investigator or his/her designee must return all study-related documents and devices, if supplied by Boston Scientific, unless this action would jeopardize the rights, safety, or welfare of the subjects.

18.5. *Criteria for Suspending/Terminating a Study Site*

Boston Scientific reserves the right to stop the inclusion of subjects at a study site at any time after the study initiation visit if no subjects have been enrolled for a period beyond six months after site initiation, or if the site has multiple or severe protocol violations/noncompliance without justification and/or fails to follow remedial actions.

In the event of termination of site participation, all devices and testing equipment, as applicable, will be returned to BSC unless this action would jeopardize the rights, safety or well-being of the subjects. The IRB/EC/REB and regulatory authorities, as applicable, will be notified. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

19.Clinical Trial Registration and Results Posting

This research-study is registered on http://www.ClinicalTrials.gov, as required by U.S. Law and other jurisdictions.

In Japan, Investigator shall register a summary of this research-study in one public database operated by the National University Hospital Council of Japan, the Japan Pharmaceutical Information Center, or the Japan Medical Association. Below are the lists of public database available:

- UMIN-CTR: http://www.umin.ac.jp/ctr/index-j.htm
- Iyaku Search: http://database.japic.or.jp/is/top/index.jsp
- JMA CCT: https://dbcentre3.jmacct.med.or.jp/jmactr/

Investigator shall update the registered contents appropriately according to revisions of the research-study protocol, the progress of the research-study, and shall register the results of the research-study when the research is completed.

20.Publication Policy

BSC requires disclosure of its involvement as a sponsor or financial supporter in any publication or presentation relating to a BSC study or its results. BSC will submit study results for publication (regardless of study outcome) following the conclusion or termination of the study. Boston Scientific adheres to the Contributorship Criteria set forth in the Uniform Requirements of the International Committee of Medical Journal Editors (ICMJE; http://www.icmje.org). In order to ensure the public disclosure of study results in a timely manner, while maintaining an unbiased presentation of study outcomes, BSC personnel may assist authors and investigators in publication preparation provided the following guidelines are followed.

- All authorship and contributorship requirements as described above must be followed.
- BSC involvement in the publication preparation and the BSC Publication Policy should be discussed with the Coordinating Principal Investigator(s) and/or Executive/Steering Committee at the onset of the project.

- The First and Senior authors are the primary drivers of decisions regarding publication content, review, approval, and submission.

The data, analytic methods, and study materials for this clinical trial may be made available to other researchers in accordance with the Boston Scientific Data Sharing Policy (https://www.bostonscientific.com/).

21. Reimbursement and Compensation for Subjects

21.1. *Compensation for Subject's Health Injury*

Boston Scientific will purchase an insurance policy to cover the cost of potential health injury for study subjects, if required by applicable law.

22. Bibliography

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23. Abbreviations and Definitions

23.1. *Abbreviations*

Abbreviations are shown in Table 10.

Table 10: Abbreviations

Abbreviation/Acronym	Term
AAD	Anti-Arrhythmic Drug
CABG	Coronary artery bypass grafting
CRT	Cardiac Resynchronization Therapy
CVA	Cerebral Vascular Accident
EDC	Electronic Data Capture
ICD	Implantable Cardioverter Defibrillator
ICF	Informed Consent Form
OI	Open-Irrigated
PAF	Paroxysmal Atrial Fibrillation
PE	Pulmonary Embolism
PTCA	Percutaneous transluminal coronary angioplasty
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
TEE	Trans-esophageal echocardiography
TIA	Transient Ischemic Attack

23.2. *Definitions*

Terms are defined in Table 11.

Table 11: Definitions

Term	Definition
Ablation Attempt	One or more RF ablations targeted at a single gap closure. An attempt is considered complete once isolation is tested.
Activated Coagulation/Clotting Time	ACT is a test that is used to monitor the effectiveness of high dose heparin therapy.
Arterial-Venous Fistula	Abnormal communication between an artery and a vein.
Atrio-Esophageal Fistula	A connection between the atrium and the lumen of the esophagus
ATTEMPT Subject	Any subject that signs the consent form, meets eligibility criteria and has any study device inserted into the body but does not receive RF ablation per protocol.
AV block	A conduction disturbance that results in the partial inability of an electrical impulse generated in the atria to reach the ventricles.
Blanking Period	90-day period between ablation procedure and the initiation of the Effectiveness Evaluation Period during which up to one additional ablation procedures can be performed and subjects can be prescribed antiarrhythmic drugs as determined necessary by the investigator.

Table 11: Definitions

Term	Definition
Cardiac tamponade/ perforation	The development of a significant pericardial effusion during or within 30 days of undergoing an AF ablation procedure. A significant pericardial effusion is one that results in hemodynamic compromise, requires elective or urgent pericardiocentesis, or results in a 1-cm or more pericardial effusion as documented by echocardiography.
Embolism	The sudden blocking of an artery by a clot or foreign material which has been brought to its site of lodgment by the blood current.
Enrolled Subject	A subject who is eligible for enrollment and signs an informed consent document to participate in the study.
Hematoma	A localized collection of blood, usually clotted, in an organ, space or tissue, due to a break in the wall of a blood vessel.
INTENT Subject	Any subject that signs the consent form but does not have any study devices inserted into the body. Subjects who are enrolled in the study but do not undergo ablation procedure within 60 days from consent signature date may not be reconsented and will be withdrawn from the study.
In-patient Hospitalization	Hospitalizations ≥24 hours in duration or <24 hours with medical intravenous therapy or surgical intervention
Myocardial infarction (in the context of AF ablation)	The presence of any one of the following criteria: (1) detection of ECG changes indicative of new ischemia (new STT wave changes or new LBBB) that persist for more than 1 hour; (2) development of new pathological Q waves on an ECG; (3) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
Paroxysmal Atrial Fibrillation (PAF)	Recurrent symptomatic Atrial Fibrillation that terminates spontaneously or with intervention within seven days of onset.
Pericardial Effusion	A collection of fluid or blood in the pericardial space around the heart or in pleural space around the lungs.
Pericarditis	Inflammation of the pericardium surrounding the heart. Pericarditis should be considered a major complication following ablation if it results in an effusion that leads to hemodynamic compromise or requires pericardiocentesis, prolongs hospitalization by more than 48 hours, requires hospitalization, or persists for more than 30 days following the ablation procedure.
Pneumothorax	Collapse of the lung due to an abrupt change in the intrapleural pressure within the chest cavity.
Primary Effectiveness Failure	A TREATMENT subject being an acute procedure failure, having more than one repeat procedure during the blanking period, or having any of the following between 91 days and 12 months post-procedure: • documented 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) 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

Table 11: Definitions

Term	Definition
Procedural Success	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.
Prolonged Hospitalization	Hospitalization ≥72 hours after the study procedure for reasons other than anticoagulation
Pseudoaneurysm	A dilation of an artery with disruption of one or more layers of its walls.
Pulmonary Vein Stenosis (Significant)	Pulmonary vein stenosis is defined as a reduction of the diameter of a PV or PV branch. For the primary safety endpoint of this study, significant pulmonary vein stenosis is defined as symptomatic and requiring intervention.
Pulmonary edema/heart failure	Ineffective pumping of the heart leading to an accumulation of fluid in the lungs. Typical symptoms include shortness of breath with exertion, difficulty breathing when lying flat and leg or ankle swelling.

Secondary Effectiveness Failure	A TREATMENT subject being an acute procedure failure, having more than one repeat procedure during the blanking period, or having any of the following between 91 days and 12 months post-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)
	• any of the following interventions for atrial fibrillation, or new onset of atrial flutter or atrial tachycardia between 91 days and 365 days post study procedure:
	  • Repeat procedure
	  • Cardioversion
	  • Prescribed a higher dose of any AAD documented at baseline
	  • Prescribed a new AAD not documented at baseline

Source Data	All information in original records of clinical findings, observations, or other activities in a clinical investigation, necessary for the reconstruction and evaluation of the clinical study (original records or certified copies).
Source Document	Printed, optical or electronic document containing source data. Examples: Hospital records, laboratory notes, device accountability records, radiographs, records kept at the investigation site, and at the laboratories involved in the clinical study.

Table 11: Definitions

Term	Definition
Stroke/Cerebrovascular accident (CVA)	Rapid onset of a focal or global neurological deficit with at least one of the following: change in level of consciousness, hemiplegia, hemiparesis, numbness or sensory loss affecting one side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke. Duration of a focal or global neurological deficit ≥24 hours; OR <24 hours if therapeutic intervention(s) were performed (e.g., thrombolytic therapy or intracranial angioplasty); OR available neuroimaging documents a new hemorrhage or infarct; OR the neurological deficit results in death. No other readily identifiable non-stroke cause for the clinical presentation (e.g., brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences). Confirmation of the diagnosis by at least one of the following: neurology or neurosurgical specialist; neuroimaging procedure (MRI or CT scan or cerebral angiography); lumbar puncture (i.e., spinal fluid analysis diagnostic of intracranial hemorrhage)
Symptomatic AF	Required symptom(s) of AF that were experienced by the subject, made them seek medical attention, and were concurrent with a documented episode by ECG, event monitoring and/or Holter monitor. Symptoms may have included palpitations, irregular pulse (i.e. rapid, racing, pounding, fluttering, bradycardic), dizziness, weakness, chest discomfort, and breathlessness.
Thrombus	An aggregation of blood factors, primarily platelets and fibrin with entrapment of cellular elements, frequently causing vascular obstruction at the point of its formation.
Thromboembolism	The blockage of a blood vessel lumen by air or solid material such as device fragments, blood clot or other tissues that have migrated from another anatomic site.
Transient Ischemic Attack (TIA)	New focal neurological deficit with rapid symptom resolution (usually 1 to 2 hours), always within 24 hours; neuroimaging without tissue injury
TREATMENT Subject	Any subject that signs the consent form, meets eligibility criteria and has the specified study devices inserted into the body and undergoes protocol specific treatment for the intended disease.
Vagal Nerve Injury/Gastroparesis	Vagal nerve injury is defined as injury to the vagal nerve that results in esophageal dysmotility or gastroparesis. Vagal nerve injury is considered to be a major complication if it prolongs hospitalization, requires hospitalization, or results in ongoing symptoms for more than 30 days following an ablation procedure
Vascular access complications	Development of a hematoma, an AV fistula, or a pseudoaneurysm. A major vascular complication is defined as one that requires intervention, such as surgical repair or transfusion, prolongs the hospital stay, or requires hospital admission.

24.Appendices

24.1. *Quality of Life Instruments*

Clinical trials increasingly recognize the value of including patient reported outcome measures in their design. To understand the impact of atrial fibrillation ablation procedures on patient's quality of life, the quality of life instruments used for the trial will be the EQ-5D-5L for a generic questionnaire and the AFEQT for disease specific. Subjects will be asked to complete the questionnaires at the Enrollment visit as well as at the three, six, and 12 month follow-ups.

The EQ-5D, generic quality of life measure, will be used to assess health utilities. It is a descriptive system of health-related quality of life states consisting of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) each of which can take one of five responses. The responses record five levels of severity (no problems/slight problems/moderate problems/severe problems/extreme problems) within a particular EQ-5D dimension.

The Atrial Fibrillation Effect on Quality of Life (AFEQT) was developed to evaluate disease-specific quality of life for patients with atrial fibrillation. The 20-item questionnaire is subdivided into three domains: symptoms, daily activities, and treatment concerns with responses provided on a seven-point Likert scale.

24.2. *Clinical Trial Organization*

Any Clinical Trial Organization used will be documented and available on a separate document.