Clinical Evaluation of the StablePoint Catheter and Force-Sensing System for Paroxysmal Atrial Fibrillation

NEwTON AF

PC053

CLINICAL INVESTIGATION PLAN

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Revision Version	Protocol Date	Template number and version	Protocol Section Modified	Summary of Changes	Justification for Modification
A	July 2020	90702637, Rev/Ver AM	N/A	Initial Release	N/A
B	October 2020	90702637, Rev/Ver AO	Throughout	Modifications according FDA IDE review, application # G200215, 28 Aug 2020 and additional updates to provide further clarification.	Modifications according FDA IDE review, application # G200215, 28 Aug 2020
C	December 2020	90702637, Rev/Ver AO	Throughout	Modifications according FDA IDE review, application # G200215, 06 Nov 2020, updates to align with new BSC template and additional updates to provide further clarification.	Modifications according FDA IDE review, application # G200215, 0206 Nov 2020
C	February 2021	90702637, Rev/Ver AO	Statistical	Modifications according FDA IDE review, application # G200215, 09 Jan 2021.	Modifications according FDA IDE review, application # G200215, 09 Jan 2021.

2. Protocol Synopsis

Clinical Evaluation of the StablePoint Catheter and Force-Sensing System for Paroxysmal Atrial Fibrillation (NEwTON AF)	
Study Objective(s)	To demonstrate the safety and effectiveness of the IntellaNav StablePoint Catheter and Force Sensing System with DIRECTSENSE for treatment of drug refractory, recurrent, symptomatic Paroxysmal Atrial Fibrillation (PAF).
Planned Indication(s) for Use	The IntellaNav StablePoint Catheter System, when used with a compatible Radiofrequency Controller and Irrigation Pump, is indicated for: • Cardiac electrophysiological mapping • Delivering diagnostic pacing stimuli • RF ablation of sustained or recurrent type I atrial flutter in patients age 18 years or older • Treatment of drug refractory, recurrent, symptomatic, Paroxysmal Atrial Fibrillation in patients age 18 years or older, when used with a compatible mapping system Treatment will occur according to the approved indication for use within each geography and the defined inclusion/exclusion criteria within this protocol.
Test Device and sizes, if applicable	The test devices for the study (henceforth called IntellaNav StablePoint Catheter System) include: • IntellaNav StablePoint Catheter, enabled for Force and DIRECTSENSE™ • IntellaNav StablePoint Catheter Cable • IntellaNav StablePoint Connection Box • Force Computation Software Module
Control Device	There are no control devices in this study.
Study Design	The NEwTON AF study is a multi-center, global, prospective, single arm study to establish the safety and effectiveness of the IntellaNav StablePoint Catheter and Force-Sensing System in subjects with symptomatic, drug refractory, recurrent paroxysmal atrial fibrillation. The study will be conducted in North America, Europe and Asia Pacific.

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	A 6-month endpoint analysis is planned and will be conducted after all 299 TREATMENT subjects have completed 30 days of follow up and 183 TREATMENT subjects have completed their 6-month follow-up. If effectiveness is not demonstrated at the 6-month endpoint analysis, then it may be re-evaluated at the 12-month endpoint analysis. All subjects undergoing the index procedure with the study devices will be followed up to 12 months.
Planned Number of Subjects	A minimum of 299 subjects treated with the IntellaNav StablePoint Catheter System (TREATMENT subjects) will be enrolled in the study. Subject enrollment will stop once approximately 299 subjects are accrued.
Planned Number of Investigational Sites / Countries	Up to 50 centers in North America, Europe and Asia-Pacific may participate in this study. Approximately 5 centers in Europe and approximately 3 centers in Asia-Pacific are planned. A minimum of 50% of the total subjects (150 out of the 299 enrolled subjects) and a minimum of 50% of the sites will be selected from the U.S. No study site will be allowed to contribute more than 15% for the first 183 TREATMENT subjects (27 subjects/center) and then once 183 subjects are enrolled, no more than 15% of the remaining subject enrollment (44 subjects/center) of the total required enrollment.
Primary Safety Endpoints	**Primary Safety Endpoint at 30 Days** The primary safety endpoint at 30 days is defined as the safety event-free rate at 30 days post-procedure. Primary safety events at 30 days will consist of a composite of the following serious procedure-related and/or device-related adverse events. Events will be counted through 7 days post index procedure or hospital discharge, whichever is later, unless denoted as events counting through 30 days post index procedure. • Death • Myocardial infarction (MI) • Vagal Nerve Injury/Gastroparesis • Transient ischemic attack (TIA) • Stroke/Cerebrovascular accident (CVA) • Thromboembolism • Pericarditis • Cardiac tamponade/perforation* • Pneumothorax

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- Major vascular access complications
- Pulmonary edema/heart failure
- AV block**
- Atrial esophageal fistula*
- Severe pulmonary vein stenosis (≥70% reduction in the diameter of the PV or PV branch from baseline)*

*Atrial esophageal fistula, cardiac tamponade/perforation and severe pulmonary vein stenosis occurring up to 30 days post-index-procedure will count as primary safety endpoint events

**AV block not attributable to medication effect or vasovagal reaction.

Primary Safety Endpoint at 12 Months

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

Primary safety events at 12 months will consist of a composite of the following serious procedure-related and/or device-related adverse events.

The following events will be counted through 7 days post index procedure or hospital discharge, whichever is later:

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

The following events will be counted through 30 days post index procedure:

- Cardiac tamponade/perforation

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	And the following events will be counted through 12 months post index procedure: • Atrial esophageal fistula • Severe pulmonary vein stenosis (≥70% reduction in the diameter of the PV or PV branch from baseline) • Persistent phrenic nerve palsy** * AV block not attributable to medication effect or vasovagal reaction. **A non-recovered phrenic nerve palsy at 12 months occurring post index procedure will count as a chronic primary endpoint. The study will collect information on phrenic nerve palsy observed before the end of the index procedure and, in case of occurrence, will track information for potential recovery during the study visits.
Primary Effectiveness Endpoints	**Primary Effectiveness Endpoint – Acute Procedural Success** The primary effectiveness endpoint of acute procedural success is defined as the achievement of electrical isolation of all PVs using the IntellaNav StablePoint Catheter only. Electrical isolation of a PV is demonstrated by entrance block after a 20-minute waiting period. If exit block testing is performed, the PV will only be considered isolated if both entrance and exit block testing was successful. **Primary Effectiveness Endpoint at 6 Months** This primary effectiveness endpoint at 6 months is defined as the primary effectiveness event-free rate at 6 months post-procedure. Primary effectiveness events determining a failure are defined as: • Acute procedural failure • Use of amiodarone post index procedure • Use of non-study ablation catheter in the index procedure or in a repeat procedure during the blanking period • More than one repeat procedure during the blanking period (90 days post index procedure) • Surgical ablation of Atrial Fibrillation (AF)/Atrial Tachycardia (AT)/Atrial Flutter (AFL) post index procedure • Documented atrial fibrillation, or new onset of atrial flutter or atrial tachycardia between 91 days and 183* days post index procedure captured by one of the following methods:

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	• ≥ 30 seconds in duration recording from the study specific event monitor or Holter Monitor • ≥ 10 seconds 12-lead Electrocardiography (ECG) • Any of the following interventions for atrial fibrillation, or new onset of atrial flutter or atrial tachycardia between 91 days and 183* days post index procedure: • Repeat procedure • Electrical and/or pharmacological cardioversion • Prescribed any AAD** *If evaluating the primary effectiveness endpoint at 12 months, then primary effectiveness events will include events seen through 365 days post index procedure. **AADs for endpoint will consist of all Class I/III, including Amiodarone, and any Class II/IV medications taken for control of atrial fibrillation (AF)/Atrial tachycardia (AT)/Atrial flutter (AFL) recurrence. **Primary Effectiveness Endpoint at 12 Months** This primary effectiveness endpoint at 12 months is defined as the primary effectiveness event-free rate at 12 months post-procedure.
Secondary Endpoints	Secondary Endpoints include the following: • Secondary Safety Endpoint – SAE and AE Rates • Secondary Effectiveness Endpoint 1 – New or Increased Dose of AAD • Secondary Effectiveness Endpoint 2 – Single Procedure Success defined as freedom from primary effectiveness failure without a repeat procedure • Secondary Effectiveness Endpoint 3 – Symptomatic Recurrence: freedom from documented symptomatic AF/AT/AFL recurrence
Additional Endpoints	Other additional endpoints and analysis include, but are not limited to: • Changes in the quality of life measures (AFEQT and EQ-5D-5L) between baseline and 12 months follow up • Total RF time for the index procedure (defined as the summation of all RF application durations) • Total number of RF applications • Total fluoroscopy time for the index procedure

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	• Total index procedure time • Freedom from recurrence of individual types of atrial arrhythmias between 91 and 365 days from index procedure: 1) AF 2) AT 3) AFL • Freedom from cardiovascular hospitalization at 12 months • Quantification of parameters used during RF Application including RF power, RF duration, contact force and Local Impedance via DIRECTSENSE™ technology • Descriptive summaries of primary safety and effectiveness endpoints at 12 months using the data available at the time of the 6-month analysis • The predicted probability of success for the primary effectiveness endpoint at 12 months based off the data available at the time of the 6-month analysis.
Method of Assigning Subjects to Treatment	Any subject that signs the consent form, meets eligibility criteria, has the study device inserted into the body and receives ablation therapy will be assigned to the TREATMENT group.
Follow-up Schedule	Subjects will complete a pre-discharge visit, 1-month, 3-month, 6-month, and 12-month visit.
Study Duration	Enrollment is expected to be completed in approximately 12 months; therefore, the total study duration is estimated to be approximately 24 months.
Participant Duration	The study duration for each subject is expected to be approximately 12 months.
Inclusion Criteria	1. History of recurrent symptomatic Paroxysmal Atrial Fibrillation (PAF), defined as atrial fibrillation (AF) that terminates spontaneously or with intervention (either procedure or drug therapy) within seven days of onset. Minimum documentation includes the following: o a physician's note indicating recurrent self-terminating atrial fibrillation (AF) which includes at least two

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	symptomatic AF episodes in the patient's history within the last 6 months prior to enrollment, and o any electrocardiographically documented AF episode within 12 months prior to enrollment (see **Table 10-3**). 2. Subjects who are eligible for an ablation procedure for PAF according to 2017 HRS expert consensus statement on catheter ablation of atrial fibrillation; 3. Subjects refractory or intolerant to at least one class I or class III antiarrhythmic medication or contraindicated to any class I or III medications; 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 18 years or above, or who are of legal age to give informed consent specific to state and national law.
Exclusion Criteria	Subjects will be excluded from the study if they meet any of the following criteria: 1. Subjects with New York Heart Association (NYHA) Class III or IV heart failure $\leq$ 180 days prior to enrollment 2. Left atrial diameter $\geq$ 5.0 cm or left atrial volume >50 ml/m² indexed based on the most recent echocardiography+ 3. Left ventricular ejection fraction < 35% based on the most recent echocardiogram + 4. Continuous AF lasting longer than seven (7) days 5. Subjects who have undergone any previous left atrial cardiac ablation (RF, Cryo, surgical) 6. Atrial fibrillation secondary to electrolyte imbalance, thyroid disease, or reversible or non-cardiac cause 7. Subjects who have undergone any cardiac ablation or any surgery within 30 days prior to enrollment 8. Currently implanted with a pacemaker, ICD, CRT device, or an implanted arrhythmia loop recorder 9. Active systemic infection 10. Unstable angina or ongoing myocardial ischemia 11. Myocardial Infarction (MI) within 90 days prior to enrollment

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	12. Evidence of myxoma, left atrial thrombus or intracardiac mural thrombus[++] 13. Previous cardiac surgery (i.e. ventriculotomy, atriotomy, CABG, PTCA, PCI, coronary stenting procedures) ≤ 90 days prior to enrollment. 14. Severe valvular disease, including mechanical prosthetic mitral or tricuspid heart valves (patients with successful mitral valve repair allowed – annular ring constitutes repair); 15. Any prior history of documented cerebral infarct, TIA or systemic embolism [excluding a post-operative deep vein thrombosis (DVT)] ≤180 days prior to enrollment 16. Moderate or severe mitral stenosis (severity assessed on the most recent TTE ≤180 days prior to enrollment. Defined as pulmonary artery systolic pressure >30 mmHg) 17. Presence of left atrial appendage closure device 18. Interatrial baffle, closure device, patch, or patent foramen ovale (PFO) occluder 19. Subjects who, in the judgment of the investigator, have a life expectancy of less than two (2) years 20. Women of childbearing potential who are, or plan to become, pregnant during the time of the study (method of assessment upon investigator's discretion) 21. Amiodarone use within 60 days prior to enrollment 22. Any carotid stenting or endarterectomy 23. Stage 3B renal disease or higher (estimated glomerular filtration rate, eGFR <45 mL/min) 24. Known coagulopathy disorder (e.g. von Willebrand's disease, hemophilia) 25. Any known contraindication to an AF ablation 26. Any known contraindication for anticoagulation (e.g. patients unable to receive heparin or an acceptable alternative to achieve adequate anticoagulation) 27. Vena cava embolic protection filter devices and/or known femoral thrombus that prevents catheter insertion from the femoral approach 28. Known sensitivity to contrast media (if needed during the procedure) that cannot be controlled with pre-medication 29. Rheumatic Heart Disease 30. Presence of intramural thrombus, tumor or other abnormality that precludes vascular access, or manipulation of the catheter

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	31. Subjects unable or unwilling to complete follow-up visits and examinations for the duration of the clinical study 32. Subjects who are currently enrolled in another investigational study or registry that would directly interfere with the current study, except when the subject is participating in a mandatory governmental registry, or a purely observational registry with no associated treatments; each instance must be brought to the attention of the sponsor to determine eligibility. *+LVEF and LA diameters obtained ≤180 days prior to enrollment will be acceptable, unless a cardiac event has occurred (e.g. MI) between the date of the exam and the enrollment date. In this case, a new echocardiogram (trans-thoracic or trans-esophageal, or intracardiac echo) must be performed to confirm eligibility prior to performing ablation. If no recent (≤180 days prior to enrollment) echocardiogram is available at the time of the enrollment, a new echocardiogram must be performed either prior to enrolling the patient into the study or post-consent to confirm patient's eligibility prior to performing the ablation. For TTE, LA anteroposterior diameter measured by M-mode from the parasternal long-axis view will be used. If both LA diameter and volume are available and at least one of them meets the exclusion criteria, the subject is considered ineligible for the study.* *++The absence of thrombus must be confirmed by means of a trans-esophageal echocardiogram (TEE) within 48 hours prior to the procedure or Intracardiac Echography (ICE) during the procedure in subjects not adequately anticoagulated per **Section 10.4.2.** If a thrombus is observed, the subject no longer meets eligibility criteria and should be considered "Consent Ineligible".*
Statistical Methods	
Primary Statistical Hypotheses	**Hypothesis for Primary Safety Endpoint at 30 Days** • Ho: The primary safety endpoint event-free rate at 30 days post procedure ≤ 90% • Ha: The primary safety endpoint event-free rate at 30 days post procedure > 90% **Hypothesis for Primary Safety Endpoint at 12 Months** • Ho: The primary safety endpoint event-free rate at 12 months post procedure ≤ 89% • Ha: The primary safety endpoint event-free rate at 12 months post procedure > 89% **Hypothesis for Primary Effectiveness Endpoint – Acute Procedural Success**

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	• Ho: The acute procedural success rate ≤ 92% • Ha: The acute procedural success rate > 92% **Hypothesis for Primary Effectiveness Endpoint at 6 Months** : • Ho: The 6-month primary effectiveness event-free rate ≤ 60% • Ha: The 6-month primary effectiveness event-free rate > 60% **Hypothesis for Primary Effectiveness Endpoint at 12 Months** • Ho: The 12-month primary effectiveness event-free rate ≤ 50% • Ha: The 12-month primary effectiveness event-free rate > 50%
Statistical Test Methods	**Statistical Methods for Primary Safety Endpoints** The primary safety event-free rates at 30 days and 12 months will be calculated using Kaplan-Meier methodology. Subjects who withdraw from the study without experiencing an event will be censored on the date of their last study visit. The 95% one-sided lower confidence limit of the observed primary safety event-free rate will be compared to the performance goal (90% at 30 days, and 89% at 12 months). 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. **Statistical Methods for Primary Effectiveness Endpoint – Acute Procedural Success** The 97.5% one-sided Clopper-Pearson lower confidence limit of the observed acute procedural success rate will be calculated. If the lower confidence limit is greater than the performance goal of 92%, the null hypothesis will be rejected. **Statistical Methods for Primary Effectiveness Endpoints at 6 and 12 Months** The primary effectiveness event-free rates at 6 and 12 months will be calculated using Kaplan-Meier methodology. Subjects who withdraw from the study experiencing an event will be censored on the date of their last study visit or arrhythmia/event monitor use, whichever is later. The 97.5% one-sided lower confidence limit of the observed primary effectiveness event-free rate will be compared to the performance goal (60% at 6 months, and 50% at 12 months). The lower confidence limit

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	will be calculated as the pointwise confidence limit using the log-log methodology. If the lower confidence limit is greater than the performance goal, the null hypothesis will be rejected.
Sample Size Parameters	The sample size estimate for each endpoint 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 calculations for the primary safety endpoint analyses:

Assumptions	Primary Safety at 30 Days	Primary Safety at 12 Months
Expected rate	95%	94%
Performance goal	90%	89%
Attrition (per year)	5%	10%
Significance level (one-sided)	5%	2.5%
Power	90%	80%
Sample size	252	299

The overall study sample size of 299 TREATMENT subjects is driven by the analysis of the primary safety endpoint at 12 months. The following assumptions were used in the primary effectiveness endpoint sample size calculations:

Assumptions	Primary Effectiveness – Acute Procedural Success	Primary Effectiveness at 6 Months	Primary Effectiveness at 12 Months
Expected rate	98%	72%	60%
Performance goal	92%	60%	50%
Attrition (per year)	0%	10%	10%
Significance level (one-sided)	2.5%	2.5%	2.5%

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	<table><tr><td>Power</td><td>90%</td><td>90%</td><td>90%</td></tr><tr><td>Sample size</td><td>160</td><td>183</td><td>288</td></tr></table> *12-Month Effectiveness will only be evaluated as a secondary endpoint if the primary effectiveness objective is fulfilled at the 6-Month Primary Effectiveness analysis.
Arrhythmia Monitoring Strategy	This study will employ a rhythm surveillance monitoring strategy consistent with the recommendations in the 2017 HRS expert consensus statement on catheter and surgical ablation of atrial fibrillation. A wearable arrhythmia/event monitor will be used to assess atrial arrhythmia recurrence (including unscheduled visits for symptomatic atrial arrhythmias and 24-hour Holter monitoring at the 6- and 12-month follow-up). Within the first 90 days after the index ablation procedure, TREATMENT subjects will be instructed to transmit all symptomatic episodes for detection and treatment of early recurrences. All TREATMENT subjects will be provided with an event monitor and required to submit at least two transmissions every month after their 3-month follow-up visit until their 12-month follow-up. All TREATMENT subjects will be provided with a 24-hour Holter Monitor at the 6-month follow-up visit where they will be required to submit their heart rhythms. Another 24-hour Holter is required at the 12-month follow-up visit. A core lab will be utilized for reviewing electrocardiographic recordings from the surveillance monitoring, inclusive of data from the wearable arrhythmia/event monitors and in-hospital ECGs.

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4. Introduction

4.1. Background

Atrial fibrillation (AF) is the most commonly encountered sustained cardiac arrhythmia in clinical practice (2). It currently affects approximately 2.3 million people in North America (3) and 4.5 million people in Europe (4, 5, 6). In addition, 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 (7, 8, 9).
It is not anticipated that the device under investigation will treat a Medicare population different than the demographics found in the investigators' general population for this same condition, including populations eligible for Medicare due to age (e.g., 65 years or older), disability, or other eligibility status. Among Medicare beneficiaries, incident AF is common and increases as individuals age with incidence rates per 1000 person-years reported at ages 70-74 of 18.8, increasing to 28.8 for persons age 75-79 and 38.3 of persons age 80-84. Similarly, the overall prevalence among Medicare beneficiaries age 70-74 is about 6% increasing to over 13% for individuals 80 years of age and older. (10).

Because the prevalence of AF increases with age, the results of this study are expected to be generalizable to the Medicare eligible population primarily due to program eligibility due to age (e.g., 65 years or older).

AF causes symptoms that impair quality of life, increases the risk of stroke fivefold and also increases mortality. There are multiple therapies in current use for the treatment of AF; however, it is recognized that many of these therapies are suboptimal for most patients. Treatment options include medical management, pacing, cardioversion, implantable devices, surgery, and ablation therapy to eliminate the arrhythmia (11). It has been increasingly recognized that focal pulmonary vein triggers of AF can account for 80 to 95 percent of paroxysmal cases that are drug resistant. As outlined in the 2017 Heart Rhythm Society (HRS) consensus document (12), "electrical isolation of the PVs is now recognized as the cornerstone of AF ablation. At most centers where AF ablation is performed, a strategy of creating a series of point-by-point radiofrequency lesions that encircle the PVs is used."

In the current clinical state of the art, power, time, and tissue contact are monitored to balance the formation of effective transmural lesions with the risk of adverse effects (cardiac perforation, steam pops, and thrombus formation). When using conventional ablation catheters, like the predecessor catheters, tissue contact is determined by surrogate parameters like tactile feel, generator impedance, intracardiac electrogram amplitude, catheter position on a visualization system relative to the anatomy or using ancillary products like intracardiac echo. Catheter to tissue contact has been shown to be a determinant of individual lesion dimensions and adverse events (i.e. steam pop, thrombus or char) via ex vivo tissue preparations and in vivo pre-clinical were incorporated into the distal tip of cardiac ablation catheters (13-16). With the introduction of force sensing catheters, physicians gained access to additional feedback on the mechanical coupling between the catheter tip and tissue which provides additional feedback for consistent RF application. The use of contact force is now a mature, state of the art technology for open irrigated ablation with several years of clinical

experience, holding great potential for improving the safety and success rates of AF ablation procedures by reducing suboptimal and excessive CF during ablation (17).

Boston Scientific (BSC) has developed the IntellaNav™ StablePoint Catheter, an 8.5F compatible, steerable, open irrigated, radiofrequency ablation catheter with multiple diagnostic electrodes that leverages the existing BSC OI platform and incrementally provides the ability to measure a force applied to the distal tip. The catheter is designed to incorporate force-sensing elements while preserving the core therapeutic functionality of the prior Blazer™ OI family of catheters (including both Blazer™ Open-Irrigated and IntellaNav™ Open-Irrigated [BOI-NOI]) relative to RF delivery, cooling performance, and maneuverability within the cardiac environment.

In addition to the contact force sensing capability, the IntellaNav™ StablePoint Catheter is also enabled to measure Local Impedance via DIRECTSENSE™ technology. Local Impedance is a measure of the impedance properties closest to the catheter distal electrode that allows for a diagnostic metric that can be used in conjunction with other clinical measures to inform the physician on catheter proximity relative to cardiac tissue and resistive heating directly under the ablation electrode of the catheter. Local impedance measured at the ablation catheter tip has been shown to provide a superior method of assessing catheter-tissue coupling compared to generator impedance in both preclinical and clinical settings (18-20). Additionally, a strong correlation has been demonstrated between local impedance drop and lesion formation preclinically (in vitro and in vivo), and in the clinical setting via pace capture (19,20). Tissue temperature changes due to local heating with application of radiofrequency (RF) energy during catheter ablation results in decreasing local electrical resistivity surrounding the RF electrode and a characteristic decrease in local impedance. Monitoring electrode impedance changes via the ablation generator can provide real-time feedback on the tissue response to RF ablation.

Both contact force sensing and local impedance capabilities implemented in the StablePoint Catheter may concur to improve ablation procedures as their complementary use can provide an advantage over the use of one metric alone. When studying the complementary nature of the two features with discrete lesions in vitro and in vivo, it resulted that the confirmation of stable mechanical contact and viewing of real-time local impedance drops enabled a significant reduction in RF time while creating a continuous linear lesion (21).

The IntellaNav StablePoint Catheter System includes the IntellaNav StablePoint Catheter and Cable, the Maestro Force Sensing Connection Box and the Force Computation Software Module. When used with the Rhythmia HDx™ Mapping System with Software 4.0.1 or greater and the BSC Cardiac Ablation System, the Force Sensing System can be used for treatment of drug refractory, recurrent, symptomatic Paroxysmal Atrial Fibrillation. The catheter system is based on BSC's Blazer™ Open-Irrigated and IntellaNav™ Open Irrigated ablation catheter platform. This platform has been investigated in the BLOCk-CTI and ZERO AF clinical trials, and have demonstrated safe and effective use.

The IntellaNav StablePoint Catheter System received CE mark on June 5, 2020 and will be commercially available in geographies that accept CE mark.

4.2. Study Rationale

The goal of any design or therapeutic strategy for AF is to restore normal sinus rhythm and to reduce or eliminate the symptoms due to rapid atrial response. RF ablation with Open-Irrigated technology has been proven to decrease the likelihood of thrombus and char formation (22), so it is deemed appropriate for safely performing ablation in the left atrium, including pulmonary vein isolation to treat AF. Additionally, the correlation between lesion size and contact force/contact time has allowed, in recent years, catheters equipped with contact force technology to become common in the ablation of the PVs.

The IntellaNav™ StablePoint Catheter is a contact force sensing ablation catheter that is part of the Blazer™ Open-Irrigated family of ablation catheters (BOI-NOI), including both Blazer™ Open-Irrigated and IntellaNav™ Open-Irrigated. The IntellaNav™ StablePoint Catheter maintains design elements key to the clinical performance of the predecessor BOI-NOI catheters while incorporating contact force sensing capability. The IntellaNav™ StablePoint Catheter provides the user with measurements of the magnitude and direction of an applied force between the distal tip electrode of the catheter and cardiac tissue when used with the IntellaNav StablePoint Connection Box and associated Force Computation Software (SW) Module, which are collectively referred to as the Force Sensing System.

Although design changes in various sections of the catheter were necessary to incorporate contact force sensing elements and to improve device manufacturability, the IntellaNav™ StablePoint Catheter maintains design characteristics of the predecessor catheters (BOI-NOI) that define the clinical performance. These characteristics include radiofrequency energy delivery, cooling performance, and device steering and maneuverability. In addition to the contact force sensing feature, BSC has included an additional feature, Local Impedance, into the IntellaNav™ StablePoint Catheter. The local impedance measurement on the IntellaNav™ StablePoint Catheter uses DIRECTSENSE™ technology and does not require additional design changes to the catheter.

Safety and performance of the IntellaNav™ StablePoint Catheter and Force Sensing System were assessed through extensive bench testing, and animal testing at the device and system level. The NEwTON AF Study will be conducted to establish the safety and effectiveness of the IntellaNav™ StablePoint Catheter and Force Sensing System for the treatment of symptomatic, drug refractory, recurrent paroxysmal atrial fibrillation. Data from this study will be used to support worldwide usage guidance and post market requirements in certain geographies.

5. Device Description

The IntellaNav™ StablePoint Catheter System is a new system developed by Boston Scientific Corporation. The system consists of the:

- IntellaNav StablePoint Catheter (Catheter) (**Section 5.1.1**)
- IntellaNav StablePoint Catheter Cable (Cable) (**Section 5.1.2**)
- IntellaNav StablePoint Connection Box (Connection Box) (**Section 5.1.3**)
- Force Computation Software Module (**Section 5.1.4**)

IntellaNav™ StablePoint Catheter System has CE certification; therefore, it will be commercially available in some of the participating countries.

5.1. IntellaNav StablePoint Catheter and Force Sensing System

The IntellaNav™ StablePoint Catheter System has a Force Sensing System that integrates with BSC's mapping and navigation system and Open Irrigated (OI) Radio Frequency (RF) Ablation System to enable the delivery of RF energy to target locations on the endocardium. The IntellaNav StablePoint Catheter is an 8.5Fr compatible linear catheter that leverages the design of the Blazer Open Irrigated and IntellaNav Open Irrigated ablation catheter platform and incrementally provides the ability to measure a mechanical force applied to the distal tip electrode and the ability to measure changes in the local impedance. All components of the Force Sensing System are required to use the catheter.

When used with a compatible mapping and navigation system, the catheter can be tracked in 3D space, display intracardiac electrograms and/or create electro-anatomical maps. An external recording system can also be used to display intracardiac electrograms or configure channels for delivering pacing stimuli. A compatible mapping and navigation system is also required for the feedback on contact force and local impedance via DIRECTSENSE™ technology. DIRECTSENSE™ is a software feature on the RHYTHMIA HDx™ Mapping System that provides a display of local impedance, which reflects tissue properties closest to the catheter distal electrode, when enabled by a compatible BSC Ablation Catheter. The Force Computation Software module is loaded on the RHYTHMIA HDx™ Mapping System, which is then used for force and DIRECTSENSE™ visualization.

In order to deliver radiofrequency energy, the Force Sensing System must be connected to a compatible RF generator and Irrigation Pump System via the Connection Box. In **Figure 5-1** below all components of the Force Sensing System are shown along with the additional compatible systems that are required for use.

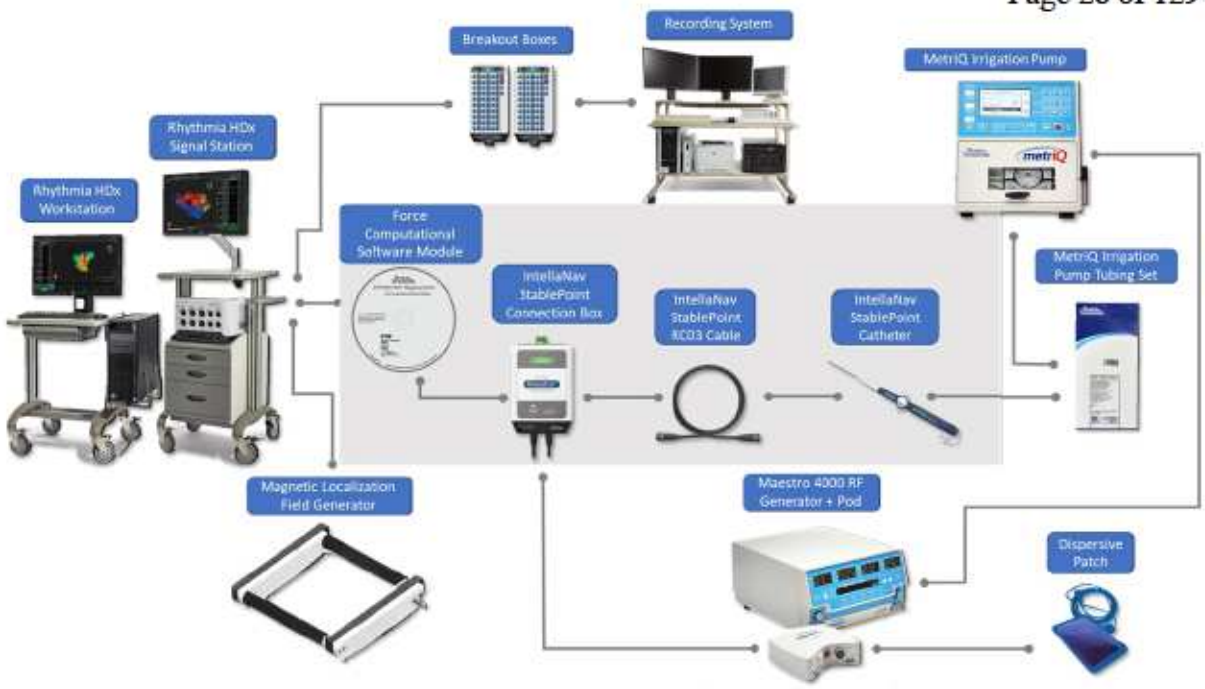

Figure 5-1: IntellaNav StablePoint Catheter and Force Sensing System with RHYTHMIA HDX™

Table 5-1 consists of the IntellaNav StablePoint Catheter System components along with the associated US UPN numbers. UPN numbers listed may differ based on geography.

Table 5-1: IntellaNav StablePoint Catheter* Components

Equipment Name	US UPNs
IntellaNav StablePoint Catheter	STD: M004IDERFS96200 K2: M004IDERFS9620K20
IntellaNav StablePoint RC03 Catheter Cable	M004IDERARC030
IntellaNav StablePoint Connection Box	M004IDERA63010
Force Computation Software Module	M004RH23250

*Investigational devices have CE certification

5.1.1. IntellaNav StablePoint Ablation Catheter

The IntellaNav StablePoint Ablation Catheter pictured in **Figure 5-2** (henceforth referred to as the IntellaNav StablePoint) is a single-use, steerable, quadripolar, open-irrigated ablation catheter designed to deliver Radiofrequency (RF) energy to the 4 mm catheter tip electrode for cardiac ablation.

Figure 5-2: IntellaNav StablePoint Ablation Catheter

The IntellaNav StablePoint shaft is 7.5Fr with 8Fr ring electrodes. The IntellaNav StablePoint is compatible with introducers or sheaths with a minimum inner diameter of 8.5Fr. The catheter is available in two curve sizes. See **Table 5-2** for more information regarding the IntellaNav StablePoint characteristics and ablation catheter parameters.

Table 5-2: IntellaNav StablePoint Catheter Parameters

StablePoint Characteristic	Value
Catheter Tip Electrode Length	4mm
Catheter Shaft Size	7.5 Fr
Catheter Tip Size	7 Fr
Ring Electrode Size	8 Fr
Compatible Sheath Size	8.5 Fr
Available curves	Standard or Large (K2)
Power/Irrigation Settings	Standby (no RF)/ 2 mL/min
	≤ 30 Watts / 17 mL/min
	> 30 Watts / 30 mL/min
Visible Force Measurement Range	Axial: 0 – 100g
	Radial: 0 – 50g

The IntellaNav StablePoint Catheter incorporates a position sensor for magnetic tracking and navigation of the catheter, when used with a compatible Rhythmia Mapping System. Additionally, the Catheter has force sensing technology embedded in the distal tip to transmit real-time feedback on the mechanical interaction between the RF tip electrode and myocardial tissue. The catheter is also enabled to measure changes in local dielectric properties in the proximity of the tip electrode via DIRECTSENSE™ technology.

By enabling DIRECTSENSE™, the IntellaNav StablePoint Catheter provides a display of local impedance that measures the dielectric properties closest to the catheter tip electrode. This diagnostic metric can be used in conjunction with other diagnostic elements (e.g., electrogram amplitude, fluoroscopy, intracardiac echocardiography, and tactile feedback) to inform the user on stability and proximity of the catheter electrodes to the endocardial surface. During the application of RF energy, the local impedance measure provides

additional feedback on tissue heating near the RF electrode as a result of RF energy. During RF application, local impedance may not represent catheter proximity or stability nor relative position of the catheter tip-to-tissue. The local impedance is displayed as a numerical widget, a power bar graphic, a tip graphic in orange, and a real-time graph (**Figure 5-3** Local impedance elements during RF ablation). All widgets are user configurable so the physician can customize display based on their preference. The value widget is updated to display the change in local impedance from the onset of ablation. The change in local impedance is displayed in orange to match the other ablation color indicators and can be displayed as an absolute, relative or percent value. Once RF energy is terminated, the real-time graph will continue to display an orange overlay to temporally indicate that ablation has occurred at previous data epochs.

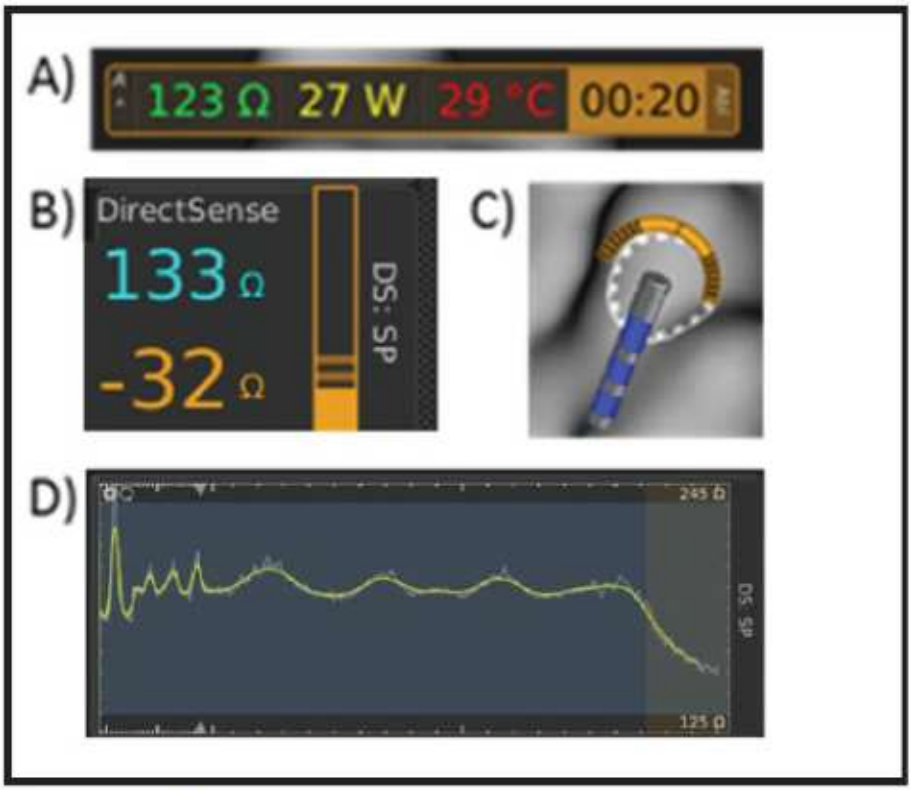

Figure 5-3: Local impedance elements during RF ablation

A) Generator parameters widget B) Numerical Value (average impedance) widget during RF C) Catheter tip graphic during RF D) Local Impedance vs. Time trace during RF

Visualization of the force information on the RHYTHMIA HDx™ Mapping System is provided in a similar set of widgets to the DIRECTSENSE™ feature; comprised of a catheter tip visualization, a force value widget, a force angle indicator, and a real-time force graph (**Figure 5-4**). All widgets are user configurable so the physician can customize display based on their preference. The real time force graph will also have an orange overlay during RF

delivery that will persist over the segment that represents the ablation while that data is in the field of view and the catheter tip will glow orange. The average contact force and the variability of contact force can be used within the context of other additional parameters (e.g. catheter position, fluoroscopy, intracardiac electrograms, and tactile feedback) to aid in the positioning of the catheter prior to and during RF delivery.

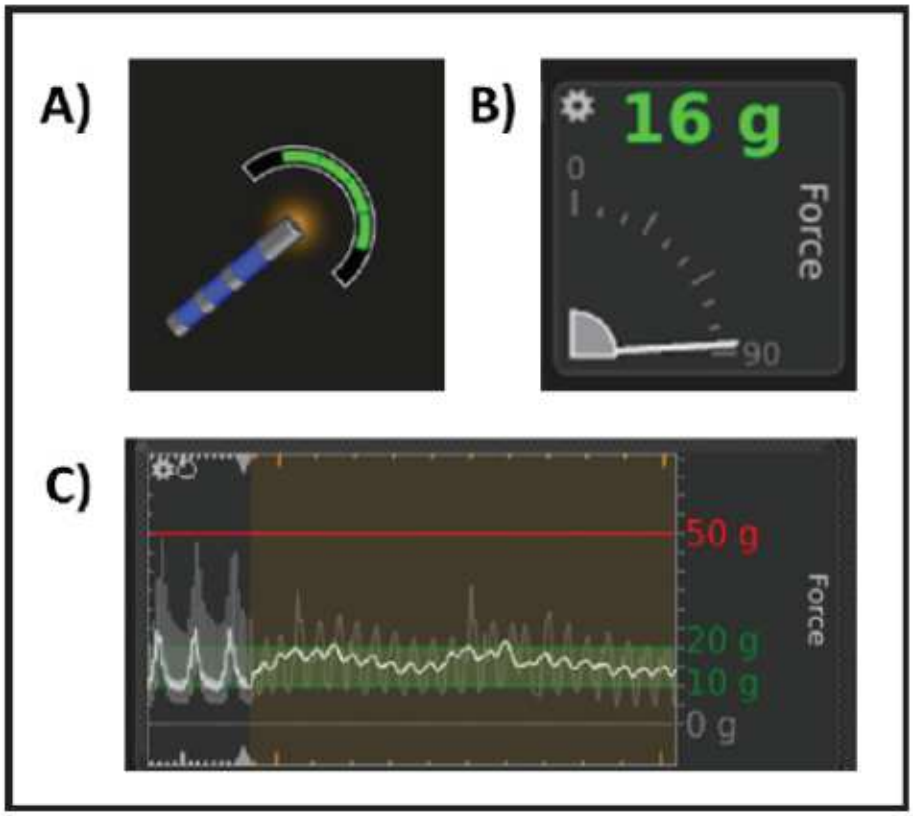

Figure 5-4: Visualization of Force on Compatible Rhythmia Mapping System

A) Catheter Tip Visualization B) Force Value Widget and Force Angle Indicator C) Force Real Time Graph with user defined range of interest and user defined high force threshold.

For ablation, the IntellaNav StablePoint is designed to be used with the Maestro 4000 RF Generator, MetriQ Irrigation Pump and MetriQ Tubing Set, the IntellaNav StablePoint Connection Box and a dispersive pad that meets the correct standard (see IFU). For mapping, navigation, and visualization of force and DIRECTSENSE™ information, the IntellaNav StablePoint is designed to be used with the RHYTHMIA HDx™ Mapping System with software 4.0.1 or greater.

The IntellaNav StablePoint incorporates 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 end of the tip electrode and mitigate overheating while the distal chamber allows the fluid to exit through six irrigation holes, thereby cooling the tip/tissue interface. A luer connection at the proximal end of the handle connects the catheter

to the Irrigation Tubing Set, allowing the Irrigation Pump to generate the flow of saline to the catheter. A thermocouple temperature sensor embedded in the tip provides feedback on the tip cooling.

The electrode segment is comprised of a tip electrode and three ring electrodes. All the electrodes can be used for recording intracardiac electrograms (EGM) or delivering pacing stimuli from external systems. The tip electrode transmits RF energy for cardiac ablation. The IntellaNav StablePoint interfaces with standard RF Generators and recording equipment through the Connection Box. The handle includes the electrical connector for the cable connection to the Connection Box and data that enables visualization of 3D position, force, and DIRECTSENSE™ on a compatible Rhythmia Mapping System. The IntellaNav StablePoint™ is to be used by physicians with training in Cardiology and a sub-specialty in electrophysiology.

5.1.2. IntellaNav StablePoint RC03 Catheter Cable

The IntellaNav™ StablePoint Catheter Cable connects the IntellaNav™ StablePoint Ablation Catheter to the RHYTHMIA HDx™ Mapping System Connection Box. The cable transmits RF energy to the IntellaNav StablePoint catheter and facilitates transmission of signals from the electrodes, force sensor, temperature sensors, location sensor, and catheter identifier. The catheter cable is a 6.6-ft- (200 cm) long flexible electrical cable with identical 41-pin locking connectors on each end. The cable is supplied sterile and should be treated as a single use device for this study.

5.1.3. IntellaNav StablePoint Connection Box

The IntellaNav StablePoint Connection Box (StablePoint Connection Box) is an accessory used with the RHYTHMIA HDx™ Mapping System to connect the IntellaNav StablePoint Catheter (via the IntellaNav StablePoint Catheter Cable) to both the Signal Station and the RF Generator. The StablePoint Connection Box is a reusable, non-sterile, and non-patient contacting.
The StablePoint Connection Box routes intracardiac signals and location and force information sensed by the ablation catheter to the mapping system and prevents RF energy from affecting catheter localization and other mapping system features. The StablePoint Connection Box also passes catheter tip temperature and catheter tip impedance information, as well as RF energy between the RF generator and ablation catheter. Additionally, the StablePoint Connection Box contains the hardware required for measuring the force from the sensors in the Catheter. When using this device, investigators should follow the standard operating procedure of the electrophysiology lab or the directions for use contained in the manufacturer's operator's manual for equipment set-up and operation.

5.1.4. Force Computation Software (SW) Module

The Force Computation SW Module interfaces with the IntellaNav StablePoint Force Sensing catheter and calculates the force magnitude and direction. It is installed on the RHYTHMIA HDx™ Mapping System Signal Station. When the Force Computation SW Module is installed, and a compatible IntellaNav StablePoint Catheter is connected to the

RHYTHMIA HDx™ Mapping System, the force visualization features become available to the user. While force computation is performed by the Force Computation SW Module, force visualization is performed by the RHYTHMIA HDx™ software version 4.0.1 or greater.

5.2. Additional Commercial Systems

The IntellaNav StablePoint Catheter System must be used with additional ancillary products to complete an EP ablation procedure.

5.2.1. RHYTHMIA HDx™

The IntellaNav StablePoint ablation catheter is designed to be used with the BSC RHYTHMIA HDx™ Mapping System (and associated accessories) for mapping and navigation, and visualization of contact force and DIRECTSENSE™ throughout an electrophysiology procedure. The RHYTHMIA HDx™ Mapping System is a catheter-based atrial and ventricular mapping system designed to acquire data from multiple electrodes in order to display 3D anatomical and electroanatomical maps of the human heart in real-time. Additionally, the RHYTHMIA HDx™ Mapping System enables the ability to track compatible catheter locations within the heart, visualize the position relative to the constructed anatomical shell, and acquires and displays intracardiac electrogram signals. The RHYTHMIA HDx™ is required for enabling the capability of 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.

Use of the RHYTHMIA HDx™ Mapping System is required for the study procedure. Prior to the start of the case, site staff must ensure that the RF Generator, IntellaMap Orion mapping catheter, patch kits, and other required or allowed equipment is properly connected to the RHYTHMIA HDx™ Mapping System per the RHYTHMIA HDx™ Hardware IFU.

5.2.2. Rhythmia Software 4.0.1 or greater

This study requires the use of Rhythmia software 4.0.1 or greater on the RHYTHMIA HDx™ Workstation. The software processes data received from the signal station and provides a user interface for system operation. It also performs ECG and intracardiac signal display, catheter localization and tracking, 3D mapping and visualization, and diagnostic stimulation routing. Rhythmia software 4.0.1 or greater with the Force Computation Software Module is used to provide force and DIRECTSENSE™ visualization for the IntellaNav StablePoint Catheter System. Additional features are enabled by Rhythmia Software 4.0.1 or greater, such as AutoTag, to enable efficient workflows based on the user's preference.

5.2.3. Generator/Pump

The catheter, cable and connection box are designed to transmit RF energy from an RF generator to the tip electrode and return feedback metrics like impedance and tip temperature

back to the RF generator. The Force Sensing System is only compatible with the BSC OI Cardiac Ablation System, which consists of the Maestro 4000 RF Generator, MetriQ™ Irrigation Pump and MetriQ™ Irrigation Tubing Set.

5.2.4. Maestro 4000 Radiofrequency Controller

The Maestro 4000 Cardiac Controller is a non-sterile RF Generator specifically designed for cardiac ablation. It produces user-selectable power-controlled or temperature-controlled RF power output in the range of 0 to 150 watts into a nominal tissue impedance of 100 ohms. It delivers RF power via a monopolar method driving current between a single active electrode at the tip of the ablation catheter and one or two dispersive pads applied on the skin. The Maestro 4000 generator interfaces with the investigational catheter via the Maestro 4000 pod (150W or 100W available depending on geography[1]) and the IntellaNav StablePoint Connection Box. Once connected, the Maestro 4000 automatically recognizes the IntellaNav StablePoint catheter (via the resistor ID) as a member of the BSC OI platform. This limits the power to a maximum of 50W and establishes power-controlled mode. When connected to the irrigation pump, the RF Generator communicates with the MetriQ™ Irrigation Pump to coordinate delivery of RF energy with irrigation flow to the catheter tip. Generator settings per RF application can be communicated to a recording system and/or a mapping system via a serial cable connection.

5.2.5. MetriQ™ Irrigation Pump

The MetriQ™ Pump is a non-sterile peristaltic pump used during RF Cardiac Ablation interventional procedures with open irrigation ablation catheters. The pump provides a single channel of continuous flow through the Tubing Set and the irrigation lumen of the IntellaNav StablePoint. The flow rate is controlled such that the fluid exits the ports in the tip electrode in a predictable manner. Three flow rates can be programmed; a standby flow rate, a low power flow rate and a high-power flow rate. When used with the Maestro 4000 in automatic mode, the generator tells the pump which of the three programmed flow rates to use based on the RF power settings for each RF application.

5.2.6. MetriQ™ Irrigation Tubing Set

The MetriQ™ Tubing Set is a sterile, disposable tubing assembly which consists of a drip chamber with intravenous (I.V.) spike for connection to the irrigation source, a peristaltic section that is loaded around the pump head, and a standard luer fitting for connection to Boston Scientific Open-Irrigated Ablation Catheters. The tubing set is designed to operate with the MetriQ™ Irrigation Pump, for use in the administration of irrigation solution into the patient through a Boston Scientific Open-Irrigated Ablation Catheter. A four-way stopcock is included.

[1] 150W and 100W Maestro 4000 Pods are both approved devices in the EU. The 150W Maestro 4000 Pod is the only approved Maestro Pod accessory in the US.

5.2.7. IntellaMap Orion

Use of the IntellaMap Orion is required for the study procedure. This high-resolution mapping catheter will be used to create electroanatomical maps throughout the procedure. 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.

5.3. Intended Use and Contraindications

5.3.1. Force Sensing System Intended Use / Indications for Use within the U.S.

The StablePoint Connection Box and Cable are indicated for use with the IntellaNav StablePoint Catheter, RHYTHMIA HDx™ Mapping System, and Maestro 4000 RF Generator during an electrophysiology procedure for cardiac electroanatomical mapping, intracardiac stimulation (pacing), recording of electrical potentials, and ablations, The IntellaNav StablePoint Catheter, when used with a compatible Radiofrequency Controller and Irrigation Pump, is indicated for:

- Cardiac electroanatomical mapping
- Delivering diagnostic pacing stimuli
- RF ablation of sustained or recurrent type 1 atrial flutter in patients age 18 years or older
- Treatment of drug refractory, recurrent symptomatic, Paroxysmal Atrial Fibrillation (PAF) in patients age 18 years or older, when used with a compatible mapping system.

5.3.2. Force Sensing System Intended Use / Indications for Use outside the U.S.

The IntellaNav StablePoint Catheter and Force Sensing System received CE mark on June 5, 2020 and will be commercially available in geographies that accept CE mark. In certain geographies that do not accept CE mark, the System will be considered investigational. Please refer to the country specific Intended/Indication for Use for additional information on intended use and indications.

5.3.3. Contraindications within the U.S.

There are no contraindications for the StablePoint Connection Box, StablePoint Catheter Cable, and Computation Software Module. The IntellaNav StablePoint Catheter is contraindicated for use:

- in patients with active systemic infection
- in patients who are implanted with a mechanical prosthetic heart valve through which the catheter must pass

- in patients who are unable to receive heparin or an acceptable alternative to achieve adequate anticoagulation
- in patients who have vena cava embolic protection filter devices and/or known femoral thrombus who require catheter insertion from the femoral approach
- in patients who are hemodynamically unstable
- in patients with conditions where insertion into or manipulation in the cardiac chambers is unsafe as this may increase the risk of perforation or systemic embolic event, such as but not limited to, evidence of myxoma, Left Atrial (LA) thrombus, or intracardiac mural thrombus
- in patients with a contraindication to an invasive electrophysiology procedure where insertion or manipulation of a catheter in the cardiac chambers is deemed unsafe, such as but not limited to, a recent previous cardiac surgery: e.g., ventriculotomy or atriotomy, Coronary Artery Bypass Graft (CABG), PTCA/PCI/coronary stent procedure/unstable angina, or in patients with congenital heart disease where the underlying abnormality increases the risk of the ablation, severe rotational anomalies of the heart or great vessels
- via transseptal approach in patients with an intraatrial baffle or a foramen ovale patch
- via the retrograde transaortic approach in patients who have had aortic valve replacement

Do not use this device:

- With a long sheath with diameter less than 8.5Fr or a short introducer with diameter less than 8.5Fr
- In the coronary vasculature

5.3.4. **Contraindications outside the U.S.**

Contraindications outside of the U.S. may be different. Centers participating in geographies outside of the U.S. will follow their country specific contraindications for the IntellaNav StablePoint Catheter System based on whether it is considered investigational or commercial in their region. Please refer to the country specific contraindications for additional information in specific regions.

6. Study Objectives and Endpoints

The objective of the study is to establish the safety and effectiveness of the StablePoint Catheter and Force Sensing System for the treatment of symptomatic, drug refractory, recurrent paroxysmal atrial fibrillation (PAF). The following endpoints will be evaluated to establish the safety and effectiveness of the StablePoint Catheter and Force Sensing System for the treatment of symptomatic, drug refractory, recurrent PAF.

6.1. Primary Safety Endpoint at 30 Days

The primary safety endpoint at 30 days is defined as the safety event-free rate at 1-Month (30 days) post-procedure. Primary safety endpoint definitions are outlined in **Table 6-1**.

Primary safety events at 30 days will consist of a composite of the following serious procedure and/or device-related adverse events. Events will be counted through 7 days post index procedure or hospital discharge, whichever is later, unless denoted as events counting through 30 days post index procedure.

- Death
- Myocardial infarction (MI)
- Vagal Nerve Injury/Gastroparesis
- Transient ischemic attack (TIA)
- Stroke/Cerebrovascular accident (CVA)
- Thromboembolism
- Pericarditis
- Cardiac tamponade/perforation*
- Pneumothorax
- Major vascular access complications
- Pulmonary edema/heart failure
- AV block**
- Atrial esophageal fistula*
- Severe pulmonary vein stenosis (≥70% reduction in the diameter of the PV or PV branch from baseline)*

*Atrial esophageal fistula, cardiac tamponade/perforation and severe pulmonary vein stenosis occurring up to 30 days post-index-procedure will count as primary safety endpoint events
**AV block not attributable to medication effect or vasovagal reaction.

Table 6-1: Primary Safety Endpoint Definitions

Terms	Definitions
Atrioesophageal Fistula	An atrioesophageal fistula is defined as a connection between the atrium and the lumen of the esophagus. Evidence supporting this diagnosis includes documentation of esophageal erosion combined with evidence of a fistulous connection to the atrium, such as air emboli, an embolic event, or direct observation at the time of surgical repair. A CT scan or MRI scan is the most common method of documentation of an atrioesophageal fistula.
AV block	A conduction disturbance that results in the partial inability of an electrical impulse generated in the atria to reach the ventricles. Refers to AV block not attributable to medication effect or vasovagal reaction.
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.
Major 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.
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.
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.
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 edema/heart failure will be considered a primary safety endpoint event when an intervention is required, such as administering diuretics or a prolonged hospitalization.
Severe Pulmonary Vein Stenosis	Severe pulmonary vein stenosis is defined as a reduction of the diameter of a PV or PV branch. PV stenosis can be categorized as mild <50%, moderate 50%–70%, and severe ≥70% reduction in the diameter of the PV or PV branch. A severe PV stenosis will count towards the primary safety endpoint if it is confirmed by imaging.
Stroke/Cerebrovascular accident (CVA)	Stroke diagnostic criteria: • 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) • Stroke: (diagnosis as above, preferably with positive neuroimaging study); o Minor–Modified Rankin score <2 at 30 and 90 days o Major–Modified Rankin score ≥2 at 30 and 90 days
Thromboembolism	The blockage of a blood vessel lumen by 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.
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.

6.2. Primary Effectiveness Endpoint – Acute Procedural Success

The primary effectiveness endpoint of acute procedural success is defined as the achievement of electrical isolation of all PVs using the IntellaNav StablePoint catheter only. Electrical isolation of a PV is demonstrated by entrance block after 20 minutes waiting period. If exit block testing is performed, the PV will only be considered as isolated if both entrance and exit block testing are successful.

6.3. Primary Effectiveness Endpoint at 6 Months

The primary effectiveness endpoint at 6 months is defined as the effectiveness event-free rate at 6 months (183 days) post-procedure. If the analysis of the primary effectiveness endpoint at 6 months is not passed, then effectiveness may be re-evaluated via the primary effectiveness endpoint at 12 months, as described in **Section 6.6**.

Primary effectiveness events at 6 months are defined as:

- Acute procedural failure
  - Failure to achieve acute procedural success in the index procedure or in a repeat procedure during the blanking period.
  - Acute procedural success is defined as the achievement of electrical isolation of all PVs using the StablePoint catheter only. Electrical isolation of a PV is demonstrated by entrance block after 20 minutes waiting period. If exit block testing is performed, the PV will only be considered as isolated if both entrance and exit block testing are successful.

- Use of amiodarone post index procedure
- Use of non-study ablation catheter in the index procedure or in a repeat procedure during the blanking period
- More than one repeat procedure during the blanking period (90 days post index procedure)
- Surgical ablation of Atrial Fibrillation (AF)/Atrial Tachycardia (AT)/Atrial Flutter (AFL) post index procedure
- Documented atrial fibrillation, or new onset of atrial flutter or atrial tachycardia between 91 days and 183 days post index procedure captured by one of the following methods:
    - $\geq$ 30 seconds in duration recording from the study specific event monitor or Holter Monitor
    - $\geq$ 10 second 12-lead Electrocardiography (ECG)
- Any of the following interventions for atrial fibrillation, or new onset of atrial flutter or atrial tachycardia between 91 days and 183 days post index procedure:
    - Repeat procedure
    - Electrical and/or pharmacological cardioversion
    - Prescribed any AAD*

*AADs for endpoint will consist of all Class I/III, including Amiodarone, and any Class II/IV medications taken for control of atrial fibrillation (AF)/Atrial tachycardia (AT)/Atrial flutter (AFL) recurrence.

6.4. Primary Safety Endpoint at 12 Months

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

Primary safety events will consist of a composite of the following serious procedure-related and/or device-related adverse events.

The following events will be counted through 7 days post index procedure or hospital discharge, whichever is later:

- Death
- Myocardial infarction (MI)
- Vagal Nerve Injury/Gastroparesis
- Transient ischemic attack (TIA)
- Stroke/Cerebrovascular accident (CVA)
- Thromboembolism
- Pericarditis
- Pneumothorax
- Major vascular access complications
- Pulmonary edema/heart failure

- AV block*

The following events will be counted through 30 days post index procedure:

- Cardiac tamponade/perforation

And the following events will be counted through 12 months post index procedure:

- Atrial esophageal fistula
- Severe pulmonary vein stenosis (≥70% reduction in the diameter of the PV or PV branch from baseline)
- Persistent phrenic nerve palsy**

* AV block not attributable to medication effect or vasovagal reaction.

**A non-recovered phrenic nerve palsy at 12 months post index procedure will count as a chronic primary endpoint. The study will collect information on phrenic nerve palsy observed before the end of the index procedure and, in case it occurred, will track information for potential recovery during the study visits.

6.5. Primary Effectiveness Endpoint at 12 Months

The primary effectiveness endpoint at 12 months is defined as the event-free rate at 12 months (365 days) post-procedure.

Primary effectiveness events at 12 months are defined as:

- Acute procedural failure
    - Failure to achieve acute procedural success in the index procedure or in a repeat procedure during the blanking period.
    - Acute procedural success is defined as the achievement of electrical isolation of all PVs using the StablePoint catheter only. Electrical isolation of a PV is demonstrated by entrance block after 20 minutes waiting period. If exit block testing is performed, the PV will only be considered as isolated if both entrance and exit block testing are successful.
- Use of amiodarone post index procedure
- Use of non-study ablation catheter in the index procedure or in a repeat procedure during the blanking period.
- More than one repeat procedure during the blanking period (90 days post index procedure)
- Surgical ablation of Atrial Fibrillation (AF)/Atrial Tachycardia (AT)/Atrial Flutter (AFL) post index procedure
- Documented atrial fibrillation, or new onset of atrial flutter or atrial tachycardia between 91 days and 365 days post index procedure captured by one of the following methods:
    - ≥ 30 seconds in duration from the study specific event monitor or Holter Monitor

- ≥ 10 second 12-lead Electrocardiography (ECG)

- 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
  - Electrical and/or pharmacological cardioversion
  - Prescribed any AAD*

*AADs for endpoint will consist of all Class I/III, including Amiodarone, and any Class II/IV medications taken for control of atrial fibrillation (AF)/Atrial tachycardia (AT)/Atrial flutter (AFL) recurrence.

6.6. Study Success Criteria

Two sets of study success criteria are defined for the study. These are Study Success for PMA Submission and Overall Study success. Study Success for PMA Submission refers to the criteria that must be met prior to sPMA submission and can potentially be achieved at the time of the 6-month analysis. If Study Success for PMA Submission is not achieved at the 6-month analysis, then it may be re-assessed at 12 months. Overall Study Success refers to the success criteria assessed only after 12-month follow-up is complete. Type-I error control across all endpoint assessments is discussed in **Section 11.3.2.2**.

6.6.1. Study Success for PMA Submission

Either of the following cases must occur to achieve study success for PMA submission:

1. Study Success for PMA Submission Case 1 (all must occur):
   - Primary safety endpoint at 30 days is met.
   - Primary effectiveness endpoint – acute procedural success is met.
   - Primary effectiveness endpoint at 6 months is met.

   If the primary effectiveness endpoint at 6 months fails in Case 1 above, the primary effectiveness endpoint will be reassessed at 12 Months, as described below in Study Success for PMA Submission Case 2 and will be followed by the PMA submission at that time.

2. Study Success for PMA Submission Case 2 (all must occur):
   - Primary safety endpoint at 30 days is met.
   - Primary effectiveness endpoint – acute procedural success is met.
   - Primary effectiveness endpoint at 6 months is failed.
   - Primary effectiveness endpoint at 12 months is met.

6.6.2. Overall Study Success

Either of the following cases must occur to achieve overall study success:

1. Overall Study Success Case 1 (all must occur):
    - Primary safety endpoint at 30 days is met.
    - Primary effectiveness endpoint – acute procedural success is met.
    - Primary effectiveness endpoint at 6 months is met.
    - Primary safety endpoint at 12 months is met.
    - Primary effectiveness at 12 months is met.
2. Overall Study Success Case 2 (all must occur):
    - Primary safety endpoint at 30 days is met.
    - Primary effectiveness endpoint – acute procedural success is met.
    - Primary effectiveness endpoint at 6 months is failed.
    - Primary safety endpoint at 12 months is met.
    - Primary effectiveness at 12 months is met.

6.7. Secondary Endpoints

Secondary Endpoints include the following:

- Secondary Safety Endpoint – SAE and AE Rates
- Secondary Effectiveness Endpoint 1 – New or Increased Dose of AAD
- Secondary Effectiveness Endpoint 2 – Single Procedure Success defined as freedom from primary effectiveness failure without a repeat procedure
- Secondary Effectiveness Endpoint 3 – Symptomatic Recurrence: freedom from documented symptomatic AF/AT/AFL recurrence

6.8. Additional Endpoints

Other additional endpoints and analysis include, but are not limited to:

- Changes in the quality of life measures (AFEQT and EQ-5D-5L) between baseline and 12 months follow up
- Total RF time for the index procedure (defined as the summation of all RF application durations)
- Total number of RF applications
- Total fluoroscopy time for the index procedure
- Total index procedure time
- Freedom from recurrence of individual types of atrial arrhythmias between 91 and 365 days from index procedure: 1) AF 2) AT 3) AFL
- Freedom from cardiovascular hospitalization at 12 months
- Quantification of parameters used during RF Application including RF power, RF duration, contact force and Local Impedance via DIRECTSENSE™ technology

- Descriptive summaries of primary safety and effectiveness endpoints at 12 months using the data available at the time of the 6-month analysis
- The predicted probability of success for the primary effectiveness endpoint at 12 months based off the data available at the time of the 6-month analysis.

Table 6-2 provides an overview of the primary, secondary and additional objectives and endpoints.

Table 6-2: Overview of Primary, Secondary and Additional Objectives and Endpoints

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary Endpoints		
Evaluate the acute safety of the StablePoint Catheter	The primary safety endpoint at 30 days is defined as the safety event-free rate at 1 Month (30 days) post-procedure. Primary safety events will consist of a composite of serious procedure and/or device-related adverse events.	The list of events contributing to the primary safety endpoints was selected from those typically associated with catheter ablation of AF.
Acute procedural success	Acute procedural success is defined as the achievement of electrical isolation of all PVs using the StablePoint catheter only. Electrical isolation of a PV is demonstrated by entrance block after 20 minutes waiting period.	This is an analysis of a component of the primary effectiveness endpoint
Evaluate the effectiveness of the StablePoint Catheter, assessed initially at 6 months, with a potential evaluation at 12 months if the 6-month analysis is not passed.	Failure free rate including failure to achieve success at index or repeated procedure in blanking period, more than one repeated procedure during blanking period, documented AF/AT or new onset AFL or interventions to treat these arrhythmias after blanking period, including repeated procedures cardioversion or pharmacologic treatment. Effectiveness will be evaluated at a six-month analysis. If the 6-month analysis is not passed, an additional evaluation of primary effectiveness will be done at twelve months.	The effectiveness endpoint and the performance goal at 12 months were established based on the recommendations available in the 2017 HRS expert consensus statement on catheter and surgical ablation of atrial fibrillation. The expected rates for both the 6- and 12-month Primary Effectiveness endpoints was determined based on Boston Scientific's ZERO AF study data. The 6-month Primary Effectiveness endpoint performance goal was determined by the meta-analysis of pivotal and IDE studies on AF ablation (section 11.1.2.2)

Evaluate the 12-months safety of the StablePoint Catheter	The primary safety endpoint is defined as the safety event-free rate at 12 months post-procedure.	The list of events contributing to the primary safety endpoints was selected from those typically associated with catheter ablation of AF.
Evaluate the 12-months effectiveness of the StablePoint Catheter	Failure free rate including failure to achieve success at index or repeated procedure in blanking period, more than one repeated procedure during blanking period, documented AF/AT or new onset AFL or interventions to treat these arrhythmias after blanking period, including repeated procedures cardioversion or pharmacologic treatment.	The effectiveness endpoint and the performance goal at 12 months were established based on the recommendations available in the 2017 HRS expert consensus statement on catheter and surgical ablation of atrial fibrillation.
Secondary Endpoints		
Adverse events reporting	SAE and AE Rates	Complete overview of the safety events collected in the study
Anti-arrhythmic treatment	New or Increased Dose of AAD	This is an analysis of a component of the primary effectiveness endpoint
Single procedure success	Freedom from primary effectiveness failure without a repeat procedure.	To assess success rate after a single procedure.
Symptomatic Recurrence	Freedom from documented symptomatic AF/AT/AFL recurrence	This is an analysis of a component of the primary effectiveness endpoint
Additional Endpoints		
Quality of life assessment	Changes in the quality of life measures (AFEQT and EQ-5D-5L) between baseline and 12 months follow up	Consistent with the objective of AF ablation to improve quality of life and reduce AF-associated symptoms
Individual arrhythmia recurrence rates	Freedom from recurrence of individual types of atrial arrhythmias between 91 and 365 days from index procedure: 1) AF 2) AT 3) AFL	This is an analysis of a component of the primary effectiveness endpoint
Additional descriptive statistics	Total RF time, number of RF applications, total fluoroscopy time and index procedure time, quantification of parameters used during RF Application including RF power, RF duration, contact force and Local Impedance, Freedom from cardiovascular hospitalization at 12 months.	Analysis that are descriptive in nature and used to better characterize ablation procedure data, health data and the technology in use. The RHYTHMIA HDx™ Mapping System will be used to collect some of this information.
Provide an estimate of the likelihood of success for the primary safety and effectiveness endpoints at 12 months at the time of the 6-month analysis.	Descriptive summaries of primary safety and effectiveness endpoints at 12 months using the data available at the time of the 6-month analysis The predicted probability of success for the primary effectiveness endpoint at 12 months based off the data available at the time of the 6-month analysis.	Provides a measure of the completeness of follow-up, as well as an estimate of the likelihood of success for the primary safety and effectiveness endpoints at 12 months, at the time of the 6-month analysis.

7. Study Design

The NEwTON AF study is a multi-center, global, prospective, single arm study to establish the safety and effectiveness of the IntellaNav StablePoint Catheter and Force-Sensing System in subjects with symptomatic, drug refractory, recurrent paroxysmal atrial fibrillation. The study will be conducted in North America, Europe and Asia Pacific. A 6-month endpoint analysis is planned and will be conducted after all 299 TREATMENT subjects have completed 30 days of follow up and 183 TREATMENT subjects have completed their 6-month follow-up. All subjects undergoing the index procedure with the study devices will be followed up to 12 months.

7.1. Scale and Duration

A minimum of 299 subjects treated with the StablePoint Catheter System (TREATMENT subjects) will be enrolled in the study. Subject enrollment will stop once approximately 299 subjects are accrued. The enrollment period for this study is expected to last 12 months. Each TREATMENT subject will be followed at specified timepoints after the ablation procedure (index procedure) with a follow-up duration of 12 months. All TREATMENT subjects will be required to transmit their heart rhythms at pre-specified timepoints, as indicated the figure on the next page. Attempt subjects will only be followed for 30 days. **Figure 7-1** on the next page describes the follow-up schedule after a subject signs and dates the informed consent. A study subject's participation will be considered complete when all protocol required visits or assessments have been completed. The study duration is estimated to be 24 months (12 months enrollment with 12 months follow-up).

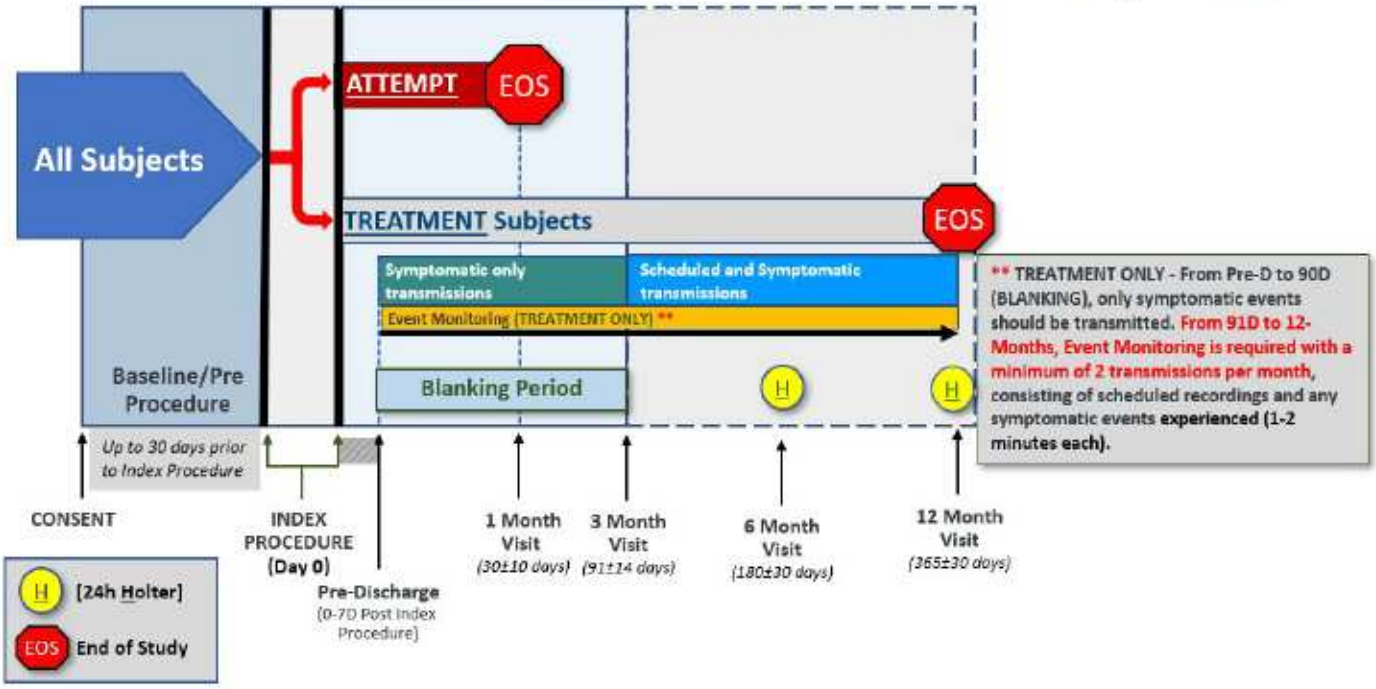

Figure 7-1: NEwTON AF Follow-up Schedule

The NEwTON AF adaptive study design, as described in **Figure 7-2** on the subsequent page, includes an analysis that will be conducted after the first 183 TREATMENT subjects have completed six months of follow up. The sPMA submission will take place if the primary effectiveness endpoint 1 analysis meets its objective. If the primary effectiveness endpoint 1 analysis is not met at 6 months, primary effectiveness will be re-assessed at 12 months. All 299 TREATMENT subjects will be followed to their 12-month follow-up visit.

Up to 50 centers in North America, Europe and Asia-Pacific may participate in this study. Approximately 5 centers in Europe and approximately 3 centers in Asia-Pacific are planned. A minimum of 50% of the total subjects (150 out of the 299 enrolled subjects) and a minimum of 50% of the sites will be selected from the U.S. No study site will be allowed to contribute more than 15% for the first 183 TREATMENT subjects (27 subjects/center) and then once 183 subjects are enrolled, no more than 15% of the remaining subject enrollment (44 subjects/center) of the total required enrollment.

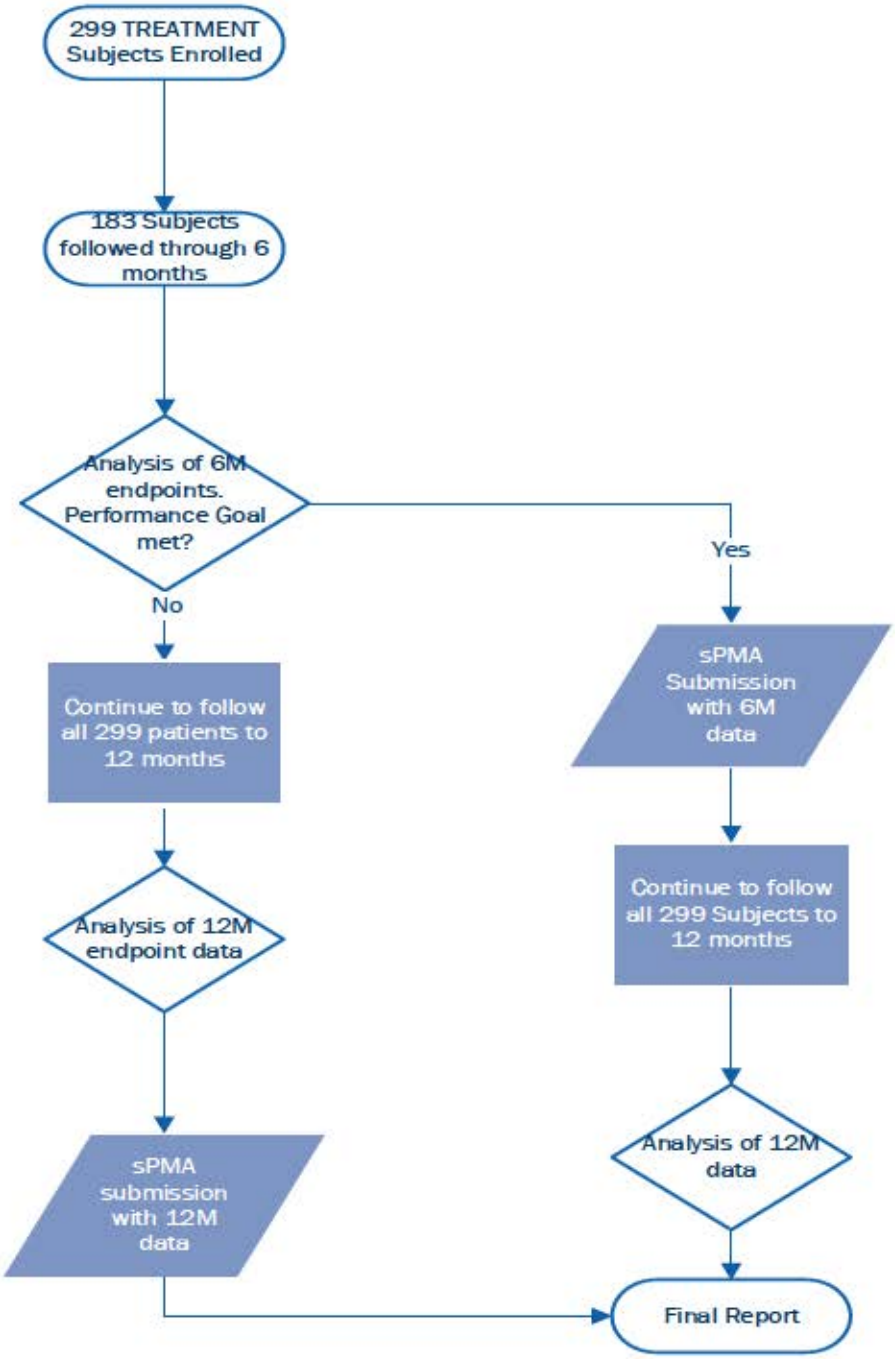

Figure 7-2: NEwTON AF Adaptive Study Design

7.2. Treatment Assignment

All screened subjects who sign the informed consent will be considered enrolled.

7.2.1. Treatment

All enrolled subjects who undergo the ablation procedure must be treated with the IntellaNav StablePoint Catheter System.

7.3. Justification for the Study Design

7.3.1. Single-Arm Study design

Boston Scientific asserts that a prospective, non-randomized trial with the IntellaNav StablePoint Catheter as treatment device and powered for standard safety and effectiveness objective performance criteria is reasonable to obtain approval of the IntellaNav StablePoint Catheter System.

The current understanding in the field of catheter ablation of PAF and presence of several devices approved by the FDA for the PAF ablation indication from four different manufacturers makes the field mature enough to consider a single arm design adequate for this study. Inherent limitations of single arm trials compared to a randomized clinical trial (RCT) will be addressed by appropriately limiting bias and confounders in the present protocol. This includes definition of inclusion/exclusion criteria to match the population enrolled in other trials on PAF ablation and taking measures for subject selection and arrhythmia recurrence surveillance.

8. Subject Selection

8.1. Study Population and Eligibility

Subjects enrolled in the NEwTON AF study will be clinically indicated for an ablation procedure for the treatment of symptomatic, drug refractory, recurrent, paroxysmal atrial fibrillation. Subjects must meet the study inclusion/exclusion criteria as outlined below in **Section 8.2** and **8.3**. The subjects selected for participation will be from the investigator's general patient population. The investigator or its designee has the responsibility for screening all potential subjects and selecting those who meet study eligibility criteria.

8.2. Inclusion Criteria

Subjects who meet all of the following inclusion criteria (see **Table 8-1**) may be given consideration for inclusion in this clinical investigation, provided no exclusion criterion (see **Table 8-2**) is met:

Table 8-1: Inclusion Criteria

Inclusion Criteria	1. History of recurrent symptomatic Paroxysmal Atrial Fibrillation (PAF), defined as atrial fibrillation (AF) that terminates spontaneously or with intervention (either procedure or drug therapy) within seven days of onset. Minimum documentation includes the following: o a physician's note indicating recurrent self-terminating atrial fibrillation (AF) which includes at least two symptomatic AF episodes in the patient's history within the last 6 months prior to enrollment, and o any electrocardiographically documented AF episode within 12 months prior to enrollment (see **Table 10-3**). 2. Subjects who are eligible for an ablation procedure for PAF according to 2017 HRS expert consensus statement on catheter ablation of atrial fibrillation; 3. Subjects refractory or intolerant to at least one class I or class III antiarrhythmic medication or contraindicated to any class I or class III medications; 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 18 years or above, or who are of legal age to give informed consent specific to state and national law.

8.3. Exclusion Criteria

Subjects who meet any one of the following exclusion criteria (**Table 8-2**) cannot be included in this study or will be excluded from this clinical study.

Table 8-2: Exclusion Criteria

Exclusion Criteria	Subjects will be excluded from the study if they meet any of the following criteria: 1. Subjects with New York Heart Association (NYHA) Class III or IV heart failure $\leq$ 180 days prior to enrollment 2. Left atrial diameter $\geq$ 5.0 cm or left atrial volume >50 ml/m² indexed based on the most recent [+]

	3. Left ventricular ejection fraction < 35% based on the most recent echocardiogram performed [+] 4. Continuous AF lasting longer than seven (7) days 5. Subjects who have undergone any previous left atrial cardiac ablation (RF, Cryo, surgical) 6. Atrial fibrillation secondary to electrolyte imbalance, thyroid disease, or reversible or non-cardiac cause 7. Subjects who have undergone any cardiac ablation or any surgery within 30 days prior to enrollment 8. Currently implanted with a pacemaker, ICD, CRT device, or an implanted arrhythmia loop recorder 9. Active systemic infection 10. Unstable angina or ongoing myocardial ischemia 11. Myocardial Infarction (MI) within 90 days prior to enrollment 12. Evidence of myxoma, left atrial thrombus or intracardiac mural thrombus[++] 13. Previous cardiac surgery (i.e. ventriculotomy, atriotomy, CABG, PTCA, PCI, coronary stenting procedures) ≤ 90 days prior to enrollment 14. Severe valvular disease, including mechanical prosthetic mitral or tricuspid heart valves (patients with successful mitral valve repair allowed - annular ring constitutes repair) 15. Any prior history of documented cerebral infarct, TIA or systemic embolism [excluding a post-operative deep vein thrombosis (DVT)] ≤180 days prior to enrollment 16. Moderate or severe mitral stenosis (severity assessed on the most recent TTE ≤180 days prior to enrollment. Defined as pulmonary artery systolic pressure >30 mmHg) 17. Presence of left atrial appendage closure device 18. Interatrial baffle, closure device, patch, or patent foramen ovale (PFO) occluder 19. Subjects who, in the judgment of the investigator, have a life expectancy of less than two (2) years 20. Women of childbearing potential who are, or plan to become, pregnant during the time of the study (method of assessment upon investigator's discretion) 21. Amiodarone use within 60 days prior to enrollment 22. Any carotid stenting or endarterectomy 23. Stage 3B renal disease or higher (estimated glomerular filtration rate, eGFR <45 mL/min) 24. Known coagulopathy disorder (e.g. von Willebrand's disease, hemophilia) 25. Any known contraindication to an AF ablation 26. Any known contraindication for anticoagulation (e.g. patients unable to receive heparin or an acceptable alternative to achieve adequate anticoagulation)

	27. Vena cava embolic protection filter devices and/or known femoral thrombus that prevents catheter insertion from the femoral approach 28. Known sensitivity to contrast media (if needed during the procedure) that cannot be controlled with pre-medication 29. Rheumatic Heart Disease 30. Presence of intramural thrombus, tumor or other abnormality that precludes vascular access, or manipulation of the catheter 31. Subjects unable or unwilling to complete follow-up visits and examinations for the duration of the clinical study 32. Subjects who are currently enrolled in another investigational study or registry that would directly interfere with the current study, except when the subject is participating in a mandatory governmental registry, or a purely observational registry with no associated treatments; each instance must be brought to the attention of the sponsor to determine eligibility. *+LVEF and LA diameters obtained ≤180 days prior to enrollment will be acceptable, unless a cardiac event has occurred (e.g. MI) between the date of the exam and the enrollment date. In this case, a new echocardiogram (trans-thoracic or trans-esophageal, or intracardiac echo) must be performed to confirm eligibility prior to performing ablation. If no recent (≤180 days prior to enrollment) echocardiogram is available at the time of the enrollment, a new echocardiogram must be performed either prior enrolling the patient into the study or post-consent to confirm patient's eligibility prior to performing the ablation. For TTE, LA anteroposterior diameter measured by M-mode from the parasternal long-axis view will be used. If both LA diameter and volume are available and at least one of them meets the exclusion criteria, the subject is considered ineligible for the study.* *++The absence of thrombus must be confirmed by means of a trans-esophageal echocardiogram (TEE) within 48 hours prior to the procedure or Intracardiac Echography (ICE) during the procedure in subjects not adequately anticoagulated per **Section 10.4.2**. If a thrombus is observed, the subject no longer meets eligibility criteria and should be considered "Consent Ineligible".*

9. Subject Accountability

9.1. Point of Enrollment

Subjects will be considered enrolled into the clinical study at the time of the study-specific informed consent form (ICF) execution. No study-related testing, procedures, etc. can take place until the Informed Consent Form (ICF) is signed and dated by the subject. Screening tests that are part of standard of care (SOC) can be used to determine pre-eligibility. Study

data from exams performed prior to consent/enrollment (e.g. TTE) will be collected as medical history data after the subject is consented/enrolled in the study.

It is the investigative site's responsibility to assess eligibility criteria before obtaining the Informed Consent Form and to document them for each screened patient in the study Screening and Enrollment Log. It is the responsibility of the delegated physician Investigator to assess final eligibility criteria prior to the subject receiving RF ablation therapy in the NEwTON AF study. If the subject is found to be ineligible prior to receiving RF ablation therapy, it must be documented.

9.2. Enrollment Controls

Subject study-specific IDs will be generated through the Electronic Data Capture (EDC) system used for this study. This database will also be utilized to provide sites with subject classification assignments once a subject has provided written informed consent. TREATMENT subjects will be counted against the enrollment ceiling for the study. Enrollment controls will be implemented to ensure no study site will be allowed to contribute more than 15% for the first 183 TREATMENT subjects (27 subjects/center) and then once 183 subjects are enrolled, no more than 15% of the remaining subject enrollment (44 subjects/center) of the total required enrollment.. In addition, BSC will communicate the process that will be followed for enrolling subjects as 299 TREATMENT subjects is approached.

9.3. 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 clinical investigation, the reason(s) shall be reported. If such withdrawal is due to problems related to investigational device safety or performance, the investigator shall ask for the subject's permission to follow his/her status/condition outside of the clinical study.

Reasons for withdrawal include but are not limited to physician discretion, subject choice to withdraw consent, lost to follow-up or death. While study withdrawal is discouraged, subjects may voluntarily withdraw from the study at any time, with or without reason, and without prejudice to further treatment. In the event a subject decides to withdraw from the study or an investigator withdraws a subject due to investigator discretion, every effort should be made to obtain full information on any on-going reportable Adverse Events/Serious Adverse Events up to the point of withdrawal. Additional data may no longer be collected after the point at which the subject has been withdrawn from the study or withdraws his/her consent, for whatever reason. Data collected up to the point of subject withdrawal may be used for study analysis, unless local regulations apply which require removal of the data. All applicable, electronic case report forms (eCRFs) up to the point of subject withdrawal and a "Subject End of Study" form (or equivalent) must be completed.

If the withdrawal is due to the investigator's discretion, the investigator is obligated to follow all open reportable Adverse Events until they can be considered as closed or chronic.

Withdrawn subjects will not be replaced.

9.4. Lost to Follow-Up

A study subject will be considered lost to follow-up if he/she fails to complete the protocol required follow-up visits and after documented attempts to reach the subject by study staff have failed.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site will attempt to contact the subject and reschedule the missed visit and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain if the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record or study file, including a copy of the certified letter if available.
- Should the subject continue to be unreachable, he or she will be considered to have withdrawn/exited from the study with a primary reason of lost to follow-up and no new data will be collected on the subject.
- All applicable, electronic case report forms (eCRFs) up to the point the subject is lost to follow-up and a "Subject End of Study" form (or equivalent) must be completed.

9.5. Subject Status and Classification

As subjects are evaluated, enrolled and treated in the study, they will be grouped into one of the following several categories. Categorization will help determine how data gathered from them will be stored and evaluated.

It is the investigational sites's responsibility to list all screened subjects, Consent Ineligible (Screening failure), Intent, Attempt and TREATMENT subjects on the Screening and Enrollment Log.

9.5.1. Consent Ineligible (Screening Failure):

A subject who has signed informed consent but is later determined to not meet eligibility criteria will be classified as "Consent Ineligible". Subjects not meeting eligibility criteria due to oversight (i.e. I/E violation) will be considered 'consent ineligible' but will also be required to enter a protocol deviation. There are no follow-up reporting requirements for consent ineligible subjects. Subjects determined to be Consent Ineligible will not be used for analysis of the endpoints. The original signed Informed Consent must be maintained in the site's subject file. A subject Identification Number (ID) will be assigned in the EDC system.

For consent ineligible subjects the following forms must be completed:

- Enrollment and End of Study eCRF must be completed
    - Relevant CRFs for study visits completed through consent ineligible determination, including device tracking, if applicable.
- Adverse Event forms for any reportable event, as defined in **Section 18.1** for any adverse event that occurs after signing the Informed Consent, up to the point of subject withdrawal

9.5.2. **Intent**

A subject who signs informed consent, meets eligibility criteria, but does not have any study devices inserted into the body will be classified as "INTENT." Subjects that are enrolled in the study but do not undergo ablation procedure within 30 days from consent signature date must not be reconsented and will be withdrawn from the study and classified as "INTENT." These subjects won't be allowed to be re-enrolled in the study.

There are no Follow Up requirements for Intent subjects. Intent subjects will not count for analysis of the endpoints. The original signed Informed Consent must be maintained in the center's patient file. A subject ID will be assigned in the EDC system.

For intent subjects, at the miniumum the following forms must be completed:

- Enrollment and baseline forms such as, but not limited to: informed consent, enrollment information and other related forms;
- End of Study form;
- Adverse Event forms for any reportable event, as defined in **Section 18.1** for any adverse event that occurs after signing the Informed Consent, up to the point of subject withdrawal

9.5.3. **Attempt**

An attempt subject is one who signs informed consent, meets eligibility criteria, and has any study device inserted into the body but does not receive ablation (RF energy) with the StablePoint Catheter System. Attempt subjects will be used for analysis of the primary safety endpoints and additional analyses of safety data, but attempt subjects will not be used for analysis of the primary effectiveness endpoints or additional analyses of effectiveness data (additional analysis include subgroup, multivariable, and center pooling analyses). Attempt subjects do not count toward the enrollment ceiling.

The original signed Informed Consent and any relevant documentation must be maintained in the site's subject file. A subject ID will be assigned in the EDC system. Attempt subjects are not allowed to be re-enrolled in the study.

Attempt subjects will be followed up to 30 days for safety. Subjects will not need to complete post-procedure arrythmia monitoring as these subjects will not count toward the analysis of the effectiveness endpoints. All applicable case report forms, per the protocol, will be completed.

For attempt subjects, at the miniumum the following forms must be completed:

- Enrollment and baseline forms such as, but not limited to: informed consent, enrollment information and other related forms;
- End of Study form;
- Protocol Deviation form
- Adverse Event forms for any reportable event, as defined in **Section 18.1** for any adverse event that occurs after signing the Informed Consent, up to the point of subject withdrawal

9.5.4. **Treatment**

Any subject that signs the consent form, meets eligibility criteria and has the specified study device inserted into the body and receives RF ablation with the StablePoint Catheter System will be classified as "TREATMENT". These subjects are followed in accordance with the follow-up schedule and are included in all study analyses. A subject ID will be assigned in the EDC system.

All applicable case report forms, per the protocol, must be completed for TREATMENT subjects. TREATMENT subjects do count towards the enrollment ceiling and will be used for analyses of the endpoints. The original signed Informed Consent and any relevant documentation must be maintained in the center's patient file.

9.6. End-of-Study Definition

A clinical trial is considered completed when subjects are no longer being examined or the last subject's last study visit has occurred.

A subject is considered to have completed the study if he or she has completed all phases of the study including the last visit or assessment as shown in the Data Collection Schedule (**Table 10-1**).

The end of the study is defined as completion of the last visit shown in the Data Collection Schedule including the 12-month follow-up visit and 24-hour Holter Monitor.

10. Study Methods

10.1. Data Collection

Each TREATMENT subject will be followed per the Data Collection Schedule defined in **Table 10-1.**

Table 10-1: Data Collection Follow-up Schedule

Procedure/ Assessment	Enrollment (up to 30 days prior to Index Procedure)	Baseline (up to 30 days prior to Index Procedure)	Index Procedure (Day 0)	Blanking Period			Effectiveness Evaluation Period			Other	
				Pre-Discharge Follow-Up (0 -7 D Post-Index Procedure)	1M Follow-Up (30 ± 10 D Post Index Procedure)	Repeat-Procedure (≤ 90 D Post- Index Procedure)	3M Follow-Up (91±14 D Post Index Procedure)	6M Follow-Up (180 ± 30 D Post Index Procedure)	12M Follow-Up (365 ± 30 D Post Index Procedure)	Unsched. Follow-Up	Repeat-Procedure (>91 D Post-Index Procedure)
Informed consent process, including informed consent signature date	X	–	–	–	–	–	–	–	–	–	–
Eligibility Criteria	X	X	X	–	–	–	–	–	–	–	–
Pregnancy Test, if necessary	–	X	–	–	–	–	–	–	–	–	–
Demographics	–	X	–	–	–	–	–	–	–	–	–
Medical history	–	X	–	–	–	–	–	–	–	–	–
Physical Assessment	–	X	–	X	X	–	X	X	X	X	–
Blood Tests	–	X[1]	–	–	–	–	–	–	–	–	–
Cardiovascular/Pulmonary Exam	–	X	–	X	X	–	–	–	–	–	–
Quality of Life Questionnaires (EQ-5D-5L and AFEQT)	–	X	–	–	–	–	X[7]	X[7]	X[7]	–	–
NIH Stroke Scale (NIHSS)	–	X	–	X[6]	–	X[6]	–	–	–	–	X[6]
Cardiac CT or MRI to assess PV diameter/stenosis	–	X	–	X[5]	X[5]	–	X[5]	X[5]	X[5]	X[5]	–
Neurology Consultation	–	–	–	X[4]	–	X[4]	–	–	–	–	X[4]
Echocardiography to assess cardiac size and function	–	X[2]	–	–	–	–	–	–	–	–	–
Screening for LA thrombus (TEE/ICE)	–	X[3]	X[3]	–	–	X[3]	–	–	–	–	X[3]
Procedural Data	–	–	X	–	–	X	–	–	–	–	X
RHYTHMIA HDx Export (Electronic Case Data)	–	–	X	–	–	X	–	–	–	–	X
12-Lead ECG	–	X	X	X	X	X	X	X	X	X	X
Phrenic Nerve Palsy Assessment				X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]

Procedure/ Assessment	Enrollment (up to 30 days prior to Index Procedure)	Baseline (up to 30 days prior to Index Procedure)	Index Procedure (Day 0)	Blanking Period			Effectiveness Evaluation Period			Other	
				Pre-Discharge Follow-Up (0 -7 D Post-Index Procedure)	1M Follow-Up (30 ± 10 D Post Index Procedure)	Repeat-Procedure (≤ 90 D Post- Index Procedure)	3M Follow-Up (91±14 D Post Index Procedure)	6M Follow-Up (180 ± 30 D Post Index Procedure)	12M Follow-Up (365 ± 30 D Post Index Procedure)	Unsched. Follow-Up	Repeat-Procedure (>91 D Post-Index Procedure)
Holter Monitor (24H)	--	--	--	--	--	--	--	X	X	--	--
Arrhythmia/Event Monitor	--	--	--	X	X	--	X	X	X	X	--
Documentation of intervention AF/AT/AFL (if any)	--	--	--	--	X	X	X	X	X	X	X
Device Deficiency Assessment	--	--	X	--	--	X	--	--	--	--	X
Medications (AAD/Anticoagulants)	X	X	X	X	X	X	X	X	X	X	X
Adverse Events Assessment	X	X	X	X	X	X	X	X	X	X	X
Protocol Deviations	X	X	X	X	X	X	X	X	X	X	X

X = required; -- = not required
Abbreviations: D = day(s), H = hour(s), NIH = National Institutes of Health, ECG = electrocardiogram, M = Month, TTE = trans-thoracic echocardiogram, TEE = trans-esophageal echocardiogram, CT = Computed Tomography, MRI = Magnetic Resonance Imaging
[1]Blood tests up to 90 days prior to enrollment
[2]TTE/TEE only required if data not available within 180 days prior to enrollment (See Section 10.6.1 for additional details on test requirements)
[3] TEE within 48 hours prior to the index procedure or ICE during the procedure. For subjects that are unable to undergo TEE, ICE may be considered as an alternative
[4] Neurology consult is only required if NIHSS scale worsens from the previous assessment. If it is suspected the patient experienced a new cerebral ischemic event,. a cerebral vascular imaging/DW-MRI scan is required and must be performed within local guidelines associated with brain MRI scan.
[5]Cardiac CT/MRI scan may be considered post-procedure if PV stenosis is suspected.
[6]NIHSS at Pre-Discharge must be performed between Day 1 and Day 7 after the procedure. All NIHSS assessments must be completed by a person certified in the administration of the NIHSS.
[7]Quality of Life Instruments (AFEQT and EQ-5D-5L) is highly recommended prior to the remaining clinical assessments (e.g., 12-lead ECG and physical assessment).
[8]Phrenic Nerve Palsy Assessment at discharge and at follow-up visits is only applicable for subjects who had phrenic nerve palsy detected during the index or repeat procedure. Subjects should be assessed per standard of care; suggested means of assessment include a sniff test or an inhalation-exhalation chest radiography of the diaphragm.

10.2. Study Candidate Recruitment, Screening and Retention

Investigators are responsible for screening all subjects and selecting those whom 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. Subjects may be given a subject stipend for their time completing study assessments.

10.2.1. Screening and Enrollment Log

A *Screening and Enrollment Log* will be maintained to document select information about candidates who fail to meet the general and specific selection criteria, including those enrolled in the study and classified either as Consent Ineligible, Intent, Attempt or TREATMENT subjects.

10.3. Informed Consent and Enrollment

Subjects who have signed and dated the Informed Consent Form are considered enrolled in the study. In order to determine eligibility of a subject, the investigator or designee needs to implement the consent process as well as verify and document the subject meets final eligibility criteria prior to receiving RF ablation therapy in the NEwTON AF study. Informed consent is required for all subjects prior to their participation in the study. No study-specific procedures can be conducted prior to the subject providing his/her consent.

The subject will 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. The original, signed consent must be kept with the subject's file and a copy must be provided to the subject.

The index procedure must be performed within 30 days post ICF signature. In case the index procedure has not been performed within this time period, the subject will be classified as Intent (see **Section 9.5.2**). The same subject cannot be considered for re-enrollment as re-enrollment is not allowed for any subjects in this study. The site will ensure that originally signed ICFs are filed in subjects' binders and the ICF process is properly documented in the medical file. Originally signed ICFs and the ICF process will be made available for review at Monitoring Visits (MVs).

For additional information regarding the informed consent process, refer to **Section 9.**

10.4. Medications

10.4.1. Anti-Arrhythmic Drugs (AAD)

10.4.1.1. AADs prior to Index Procedure

Inclusion criteria require the subject to be refractory or intolerant to at least one class I or III antiarrhythmic medication, and amiodarone stopped 60 days before enrollment. Prior and current AAD therapy will be collected in the EDC system.

If applicable, administration of amiodarone and stop date will be entered in EDC.

10.4.1.2. AADs post Index Procedure during the 90-day blanking period

Blanking period is defined as the time between Index procedure and 90 calendar days post Index procedure. Post-procedure AADs are allowed per physician's discretion during the blanking period. New AADs should not be prescribed unless considered medically necessary. If treatment with AAD is prescribed during the blanking period, it is recommended that a Class I or III AAD be selected according to the ACC/AHA/ESC 2014 Guidelines for the Management of Patients with AF. **No amiodarone use is permitted post procedure**. After the index procedure, it is recommended that the Investigator removes 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 post index procedure).

10.4.1.3. AADs post blanking period

Investigators must stop administration of AADs for any atrial tachyarrhythmia after the blanking period on the date of the 3-Month Follow-Up. If the investigator determines that the subject must be prescribed any dose of AAD* for treatment of any atrial tachyarrhythmia after the blanking period, the subject will be considered a Primary Effectiveness Failure.

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

Treatment with Class II/IV medications for conditions other than control of atrial arrhythmia recurrence is 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.

10.4.2. Anticoagulation

The following anticoagulation protocol is required for this study. An *adequate anticoagulation regimen* is represented by either approach listed in **Section 10.4.2.1** "Pre-ablation" below.

10.4.2.1. Pre-ablation

Physicians must follow either an uninterrupted anticoagulation approach (recommended) or minimally interrupted new oral anticoagulants (NOAC):

- Uninterrupted treatment with warfarin or NOAC*, requiring continued treatment including the day of the index procedure

- Minimally interrupted NOAC, requiring continued treatment but allowing to stop NOAC 12 to 24 hours before the index procedure (e.g. holding the morning dose the day of the procedure)

* Includes any approved NOAC (i.e. dabigatran, edoxaban, apixaban or rivaroxaban).

Anticoagulation guidelines that pertain to cardioversion of AF should be adhered.

If at the time of enrollment, a patient has not been anticoagulated as defined above in the pre-ablation anticoagulation, anticoagulation must be initiated and maintained from point of enrollment to the time of the index procedure. In the event that the patient has not been anticoagulated for at least 3 weeks prior to the index procedure, thrombus screening should be conducted as outlined in **Section 10.5.1**.

10.4.2.2. Intra ablation

It is recommended that heparin be administered prior to or immediately following transseptal puncture or use of the Orion mapping catheter during AF ablation procedures and the heparin is adjusted to achieve and maintain an active clotting time (ACT) of at least 300 seconds. The ACT level should be checked at a minimum of 15-minute intervals until therapeutic anticoagulation is achieved, and then at 15 to 30-minute intervals for the duration of the procedure.

10.4.2.3. After ablation

Adherence to AF anticoagulation guidelines is recommended for subjects who have undergone an AF ablation procedure, regardless of the apparent success or failure of the procedure.

Systemic anticoagulation with warfarin or a NOAC is recommended for at least 2 months post catheter ablation of AF.

Decisions regarding continuation of systemic anticoagulation more than 2 months post ablation should be based on the subject's stroke risk profile and not on the perceived success or failure of the ablation procedure.

10.5. General Study Information

10.5.1. Thrombus Screening

The absence of thrombus must be confirmed by means of a trans-esophageal echocardiogram (TEE) within 48 hours prior to the procedure or ICE during the procedure in subjects not adequately anticoagulated (as defined in **Section 10.4.2**) for at least 3 weeks prior to procedure. It is highly recommended that TEE is considered as the first choice for thrombus screening, however if subjects are unable to undergo TEE, ICE may be considered as an alternative. When screening for thrombus prior to the index procedure, ensure that the

anticoagulation approach (as described in **Section 10.4.2.1**) is followed until the day of the procedure.

If intracardiac thrombus is identified, the patient should be considered "Consent Ineligible" and withdrawn from the study.

10.5.2. **Authorized ablating physicians**

The study-related ablation procedure, from transseptal access in the left atrium until end of the ablation procedure must be performed by investigators with training in Cardiology and a sub-specialty in Electrophysiology (EP), trained to the NEwTON AF clinical protocol including use of the IntellaNav StablePoint Catheter System.

10.5.3. **De novo 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). According to subject selection criteria, all Index procedures in this study are de novo as history of previous left atrial ablation or surgical treatment for AF/ AFL/ AT constitute an exclusion criterion.

10.5.4. **Imaging**

10.5.4.1. Pulmonary Vein Imaging

Subjects must have a documented form of PV visualization for all PVs at the maximal ostial diameters prior to the ablation procedure to establish a baseline for purposes of confirming significant PV stenosis after the ablation procedure. Appropriate forms of visualization may include a Cardiac CT or MRI scan conducted as standard of care at the center. Whichever imaging is performed to assess PV stenosis for inclusion into the study or performed during the baseline assessments, it must remain the same method for assessing PV stenosis throughout the duration of the subject's participation (e.g. if PV stenosis was confirmed using a CT for an individual subject, the CT method must be used until that individual subject has exited the study). If the methodology for assessing PV stenosis is changed for an individual subject during the study, it will be considered a protocol deviation.

10.6. Visit Schedule/Assessments

10.6.1. **Enrollment/Baseline Visit**

Enrolled subjects will have baseline data collected within 30 days of Enrollment and before the Index Procedure. The Baseline Visit may be the same day as the Enrollment Visit, however the Informed Consent must be signed and dated prior to conducting any study related items.

The data collection at the Baseline Visit includes:

1) Visit date
2) Check of Eligibility Criteria*

3) Demographic data, including age at time of consent, gender, race and ethnicity, as allowable per geography
4) Physical assessment including weight, height, resting heart rate, systolic and diastolic blood pressure
5) Cardiovascular/Pulmonary Exam at Baseline must be completed by someone qualified to perform the physical assessment i.e. physician/medical doctor, nurse practitioner (NP) and/or Physician Assistant (PA) and include:
   - Lung auscultation (includes respiratory rate and respiratory rhythm)
   - Heart auscultation

6) Medical history, including, but not limited to:
   a) Evidence of symptomatic PAF in the medical history including date of last recorded episode, source of recording (Holter, ECG, etc.) and treatment history (drug, cardioversion, etc.).
   b) Underlying cardiovascular disease, if any; including but not limited to hypertension, dyslipidemia, coronary artery disease
   c) Prior history of cardiac events including acute myocardial infarction, CVA, TIA
   d) Prior surgical interventions and/or cardiac procedures
   e) Detailed history of all arrhythmias
   f) Non-cardiac comorbidities
7) The following cardiac assessments will be performed or data from existing tests/procedural information will be collected:
   a) **LVEF*, left atrial diameter* or left atrial volume* will be assessed** using **one** of the following methods:
      i) TTE/TEE (most recent, either assessed at baseline visit or from medical file if date is not ≤ 180 days prior to enrollment)
      ii) IntraCardiac Echo (ICE) during the Index Procedure
   b) **Pulmonary artery pressure**** will be assessed for patients with mitral stenosis
   c) **For PV anatomy and PV dimension assessment** using the following methods:
      i) Cardiac CT or MRI scan (most recent, either assessed at baseline visit or from medical file if date is not ≤ 180 days prior to enrollment)
   d) **For Left atrial thrombus assessment***** (see **Section 10.4** Anticoagulation and **Section 10.5.1** Thrombus Screening) using **one** of the following methods:
      i) TEE within 48 hours pre-Index Procedure, or
      ii) ICE during the Index Procedure
8) Laboratory blood tests obtained ≤ 90 days prior to enrollment will be acceptable including estimated glomerular filtration rate, eGFR.
9) A pregnancy test (method of assessment per investigators' discretion) must be performed for women of childbearing potential. A negative pregnancy test conducted as standard of care *within 7 days prior to enrollment* will be acceptable.
10) Rhythm at time of visit (by means of a 12-lead ECG)

11) Complete baseline Quality of Life Questionnaires: AFEQT and EQ-5D-5L
12) NIH Stroke Scale (NIHSS) conducted by a person certified in the administration of the NIHSS.
    a) If there is any suspicion for TIA/stroke based on the NIHSS, the subject's eligibility criteria should be re-assessed.
13) AAD history and most recent dose prior to enrollment; stop date of amiodarone (if applicable)
14) Current AAD and anticoagulation medication regimen
15) Reportable Adverse Events, if applicable
16) Protocol Deviations, if applicable

** LVEF and LA diameters obtained ≤ 180 days prior to enrollment will be acceptable, unless a cardiac event has occurred (e.g. MI) between the date of the exam and the enrollment date, otherwise a new echocardiogram (trans-thoracic or trans-esophageal, or intracardiac echo) must be performed to confirm eligibility prior to performing ablation. If no recent (≤180 days prior to enrollment) echocardiogram is available at the time of the enrollment, a new echocardiogram must be performed either prior to enrolling the patient into the study or post-consent to confirm patient's eligibility prior to performing the ablation. For TTE, LA anteroposterior diameter measured by M-mode from the parasternal long-axis view will be used. If both LA diameter and volume are available and at least one of them meets exclusion criteria, the subject is considered ineligible for the study.*

***Moderate to severe mitral stenosis, severity will be assessed as pulmonary artery systolic pressure > 30 mmHg.*

**** When assessing for Left Atrial Thrombus, it is highly recommended that TEE is considered as the first choice for thrombus screening, however if subjects are unable to undergo TEE, ICE may be considered as an alternative.*

10.6.2. **Index (Ablation) Procedure**

The Index Procedure must occur after all activities required for the Baseline Visit are completed unless ICE is being used at the start of the Index Procedure to assess final inclusion/exclusion criteria prior to delivering ablation therapy . Prior to the ablation procedure, subjects must be properly anticoagulated as described in **Section 10.4.2** and the absence of thrombus must be confirmed as described in **Section 10.5.1**. A 12-lead ECG is also required to monitor the subject during the Index Procedure.

10.6.2.1. Three-dimensional electroanatomical mapping

Prior to the ablation procedure a 3D electro-anatomical map of the left atrium is required for this study. The Rhythmia HDx™ mapping system and IntellaMap Orion mapping catheter must be used, and mapping acquisition times will be collected. A quality 3D electro-anatomical map is important to help visualize the pulmonary veins. The IntellaNav StablePoint catheter may be used to add supplemental geometry to the map at the Investigator's discretion.

10.6.2.2. Pulmonary Vein Isolation

The ablation procedure will consist of Pulmonary Vein Isolation of all pulmonary veins with the IntellaNav StablePoint Catheter System (i.e. IntellaNav StablePoint Cather, Cable and

Connection Box and the Force Computation Software Module). A point by point workflow is highly recommended, however, physicians will follow their preferred ablation workflow and standard of care while utilizing the IntellaNav StablePoint Catheter following all applicable Instructions for Use. The IntellaNav StablePoint Catheter should be inserted via Femoral access with a single or double transseptal puncture at the Investigator's discretion. Cardioversion is permitted prior to or during the ablation procedure at the Investigator's discretion and will be documented.

The IntellaNav StablePoint Catheter System must be used to complete all PV ablations, but multiple catheter curves may be utilized without a deviation or impact to acute procedural success.

Investigators are encouraged to perform Wide Area Circumferential Ablation maintaining 1-2 cm outside the PV ostium to prevent PV stenosis. Ipsilateral PVs may be isolated together or individually based on physicians' preferred workflow. Technique will be documented.

10.6.2.3. Ablation Technique

Point by point ablation utilizing the usage guidelines for Force and Local Impedance is highly recommended for all ablations. Use of a deflectable sheath is recommended but not required and will be documented if used. Both Force and Local Impedance must be visible to the user for all RF applications. Investigators may customize the configuration of the widgets on the user interface at their discretion. Use of the 'distance to nearest tag' distance indicator is highly recommended to aid in maintaining an inter lesion spacing of 6 mm or less. Standard of care practices should be employed to limit esophageal temperature rise and prevent phrenic nerve palsy. A high-power short duration ablation workflow (up to and including 50W) is permitted as long as it is consistent with the Instructions for Use. Additional care must be taken to avoid ablating at high powers on the posterior wall for extended durations.

The use of robotic system to assist with the procedure is not allowed.

10.6.2.3.1 *Use Guidance for Force*

A measure of contact force provides the user with accurate real-time feedback on the mechanical interaction between the RF tip electrode and myocardial tissue as the catheter is manipulated in the intracardiac environment. Effectiveness of RF ablation is affected by several factors including tissue thickness, tissue conductivity, tissue contact, force, stability, catheter orientation (lateral/axial), power, duration, and irrigation flow. Users should consider these factors when performing ablation and confirm effectiveness through functional endpoints such as arrhythmia termination or establishing conduction block. Contact force information should be used as additional feedback to determine effective stable contact prior to and during RF application. Additional information on the recommended use of the contact force parameter is included in the StablePoint Usage Guidance document (92564661).

Please refer to the Report of Priors and/or Investigational Brochure (depending on the geography) for additional information on the preclinical studies that have been performed on the use of Force on IntellaNav StablePoint™ Catheter.

10.6.2.3.2 *Use Guidance for Local Impedance via DIRECTSENSE™*

The DIRECTSENSE™ metric provides additional real-time feedback on local impedance changes near the RF electrode as a measure of tissue response to RF ablation. Effectiveness of RF ablation is affected by several factors including: tissue thickness, tissue conductivity, tissue contact, force, stability, catheter orientation, catheter motion (focal/drag), power, duration, and irrigation flow. Users should consider these factors when performing ablation and confirm effectiveness through functional endpoints such as arrhythmia termination or establishing conduction block. The DIRECTSENSE™ feedback should be used as additional feedback to inform the user on catheter impedance stability and proximity of the catheter electrodes to the endocardial surface prior to the onset of RF. During RF application, the relative change in DIRECTSENSE™ should be used, along with all available information, as real-time feedback on the tissue response to RF, including changes due to resistive heating. Additional information on the recommended use of the DIRECTSENSE™ parameter is included in the StablePoint Usage Guidance document (92564661).

Please refer to the Report of Priors and/or Investigational Brochure (depending on the geography) for additional information on the preclinical studies that have been performed on the use of Local Impedance on IntellaNav StablePoint™ Catheter.

10.6.2.3.3 *Use Guidance for Generator settings and pump flow rates*

The IntellaNav StablePoint catheter is designed to be used with the Maestro 4000 RF Generator when operated in power control mode. Prior to inserting the catheter, the irrigation lumen should be purged of all traces of air and the flow rate should be set to 2mL/min. Per the IFU, the irrigation rate during RF application should be set based on the RF Power according to the following table:

Table 10-2: RF Power and Flow Rate

RF Power	Minimum Irrigation Flow Rate
Standby	2 mL/min
≤30W	17 mL/min
>30W	30 mL/min

Power levels exceeding 30W may be used when transmural lesions cannot be achieved at lower energy levels but should be accompanied by an increase in irrigation flow rate to 30mL/min. Proximity to the esophagus should be considered when ablating on the posterior atrial wall. Using high power, high contact, or long durations in the region of the posterior wall may increase the risk of esophageal injury and should be avoided.

10.6.2.4. PVI Validation

10.6.2.4.1 *Confirmation of First Pass Pulmonary Vein Isolation*

After first pass encirclement of the PVs, the investigator will check for and document first pass isolation. Pulmonary vein isolation can be confirmed using the physician's standard workflow,

including but not limited to the use of the StablePoint Catheter or the Orion mapping catheter. If touch-up ablations are required to seal up gaps or to ablate potential gaps, then isolation will be confirmed post touch-up ablations. Touch-up ablations follow the same ablation strategy as outlined in the ablation technique section.

10.6.2.4.2 *Entrance/Exit Block post 20-minute waiting period*

Electrical isolation of the veins must be demonstrated by the absence of electrical propagation through the ablation lines. Electrical Isolation must be demonstrated and documented using Entrance Block for each pulmonary vein following at least a 20-minute waiting period from the last RF application in each location. Exit block verification is also recommended and may be performed per center's standard of care. If Exit Block verification is attempted, a vein will only be considered isolated if Exit Block is also demonstrated and documented on the appropriate CRF. If Exit Block is not attempted, it must be documented on the appropriate CRF and in that case, verification via Entrance Block is sufficient to confirm isolation. If isolation is not confirmed after the 20-minute waiting period, the Investigator must perform additional RF ablations to treat any gaps. Entrance Block must be re-assessed after any touch up ablations and another 20-minute waiting period is required.

10.6.2.4.3 *Validation Map (Vmap)*

Investigators are encouraged to construct a validation map (full or partial chamber) using the Rhythmia HDx™ Mapping System and IntellaMap Orion to further demonstrate the absence of electrical propagation through the ablation lines, or to identify the locations of gaps in the ablation lines where further ablation is necessary. Validation maps may be constructed at any point after the assessment of first pass isolation (i.e. during or after the 20 min waiting period). It is highly recommended that vMaps include anatomy and electrograms sampled approximately 3 cm on each side of the ablation lines so that propagation from the atrium into the veins can be clearly identified. vMaps may be created while the subject is in sinus rhythm, during pacing, or in AT if applicable. If performed, the time the vMap is initiated will be documented in the CRF. The IntellaNav StablePoint catheter may be used to add supplemental geometry (partial or full chamber) to the map at the Investigator's discretion.

10.6.2.4.4 *Adenosine & Isoproterenol*

Adenosine or isoproterenol testing is highly recommended for verification of PV isolation and may be performed per center's standard of care. If performed, it will be documented in the appropriate CRF.

10.6.2.5. Esophagus management

Esophageal temperature monitoring is highly recommended and should be performed with a commercially available esophageal probe. If a rise in temperature is noted, additional RF applications should not be performed until the temperature returns to normal to prevent accumulation of esophageal heating (e.g. heat stacking) with subsequent RF applications in the same location. An alternative to esophageal temperature monitoring is esophageal deviation, which is also allowed by this protocol. The method of esophageal management

must be documented on the appropriate CRF. Actively cooling the esophagus is not permitted per this protocol.

10.6.2.6. Phrenic Nerve Function Assessment

Provocative measures may be used such as high current pacing, when ablating on the posterior wall and near the right superior pulmonary vein to prevent damage to adjacent structures and injury to the phrenic nerve. If provocative measures are taken, they will be documented on the appropriate CRF. After completion of the ablation and prior to leaving the EP lab, fluoroscopy of diaphragm movement will be performed to assess for phrenic nerve palsy. If phrenic nerve palsy is detected, it will be documented on the appropriate CRF.

All subjects presenting with phrenic nerve palsy at the end of the index or repeat procedure will be re-assessed at the discharge visit for phrenic nerve palsy.

10.6.2.7. Additional Ablations

10.6.2.7.1 *Additional Ablations*

Additional ablation lines beyond PVI (i.e. substrate modification or LAA isolation) are not permitted per this protocol. If spontaneous triggers are found in the left atrium, they may be ablated at the discretion of the physician as long as they were not revealed by pharmacological intervention (e.g. isoproterenol or adenosine). If spontaneous atypical flutter is present, the decision to ablate is at the discretion of the physician and will be documented on the appropriate CRF. If additional ablations are required, including the CTI, BSC recommends performing the PVI first. The IntellaNav StablePoint Catheter must be used to complete all additional ablations in accordance with the IFU and the Ablation Technique Section of this protocol.

10.6.2.7.2 *Cavo-tricuspid Isthmus (CTI)*

Ablation of the CTI may be completed for subjects with a history of Type I Atrial Flutter or those in which Type I Atrial Flutter occurs during the procedure (spontaneously or induced). If CTI ablation is performed, bidirectional block will be assessed and documented on the appropriate CRF. Point by point ablation is highly recommended and physicians must use the IntellaNav StablePoint Catheter to complete all ablations in accordance with the IFU and per the Ablation Technique section of this protocol.

10.6.2.8. Data Collection at Index Procedure

The following information related to the ***index procedure*** will be collected:

- Date of procedure;
- Identification of devices:
  - IntellaNav StablePoint™ Catheter System
  - Identification of non-study devices
- Presenting rhythm at the beginning of the procedure
- Method of delivering sedation or anesthesia for the procedure

- Type of esophagus management, if any

Additional information collected during the Index Procedure includes, but may not be limited to:

- Total Procedure Time
- Total infused volume of irrigation fluid through ablation catheter
- Total LA dwell time
- Total fluoroscopy time
- Incidents of Steam Pops, if any
- Incidents of Thrombus/Char, if any
- Reportable Adverse Events, if any
- Total RF Ablation Time for PVI
- Total Number of RF applications for the PVI
- Adherence to Irrigation Flow rate instructions (per IFU)
- Ablation Technique
- Mapping Time
- Cardioversion
- Sheath Usage
- Additional parameters related to RF ablation with be exported via the export tool outlined in RHYTHMIA HDx™ Data Export Section (included but not limited to: RF duration, RF power, autotag parameters, contact force, local impedance measured by DIRECTSENSE

At the end of the PVI ablation(s), PVI will be confirmed by entrance block as a minimum requirement. VMap, exit block and adenosine testings may also be performed following the site standard practices. The following information related to ***PVI validation*** will be collected:

- First Pass isolation
- Time of Last Ablation per PV or PV pair
- Acute Isolation per PV (Entrance Block at a minimum, and Exit Block, if tested)
- Time of Acute Isolation Determination
- Was vMap performed, time it was initiated
- Final rhythm at the end of the procedure
- If Adenosine was administered
- If Isoproterenol was administered

For subjects who undergo CTI ablation as part of the Index Procedure, the following information will be collected:

- Total Procedure Time for the CTI

- Total RF Ablation Time for the CTI
- Ablation Technique
- Adherence to Irrigation Flow rate instructions (per IFU)
- Incidents of Steam Pops, if any
- Incidents of Thrombus/Char, if any
- Reportable Adverse Events, if any
- Demonstration of bidirectional block across the CTI with Methodology used (e.g. differential pacing or vMap)
- Additional parameters related to RF ablation with be exported via the export tool outlined in RHYTHMIA HDx™ Data Export Section (included but not limited to: RF duration, RF power, autotag parameters, contact force, local impedance measured by DIRECTSENSE

10.6.2.8.1 *RHYTHMIA HDx™ Data Export*

The RHYTHMIA HDx™ System collects information per RF application during a procedure including, contact force, DIRECTSENSE™, RF power, RF duration, etc. Prior to the start of the subject's index procedure, a subject ID will be entered into the RHYTHMIA HDx™ system to maintain anonymity. At the end of the procedure, the following data from the RHYTHMIA HDx™ mapping system must be exported:

- **Advanced Study Export:** This data will be saved by the site or sponsor representative onto external media provided by the Sponsor and stored in a secure location. Media will be returned to the Sponsor at the end of the study or at periodic intervals during the study and stored in a secure location.
- **Basic Ablation Data Export:** The basic ablation data export is only available on Rhythmia HDx software version 4.5 or greater. This export is a file containing a summary of RF ablation data and will be saved by the site or sponsor representative onto external media provided by the Sponsor. The file will be upload to the EDC system. If subjects are enrolled using an earlier software version that still meets the requirements of this protocol (i.e., v. 4.0.1) it will not be considered a protocol deviation but the Advanced Study Export data will need to be loaded onto a system with an upgraded software version in order to perform the Basic Ablation Data Export.

10.6.3. **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 between 0- and 7-Days post-index procedure, with the exception of the NIHSS assessment, which must occur between Day 1 and Day 7. 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 post-procedure.

Amiodarone use is NOT permitted post ablation procedure as it will be considered a primary effectiveness failure.

The data collection at Pre-Discharge includes:

1) Date of visit
2) Cardiovascular/Pulmonary Exam at discharge must be completed by someone qualified to perform the physical assessment i.e. physician/medical doctor, nurse practitioner (NP) and/or Physician Assistant (PA) and include:
   - Lung auscultation (includes respiratory rate and respiratory rhythm)
   - Heart auscultation
3) Physical assessment performed as standard of care including temperature, O_2 saturation, weight, resting heart rate, systolic and diastolic blood pressure
4) Rhythm at time of visit by means of 12-lead ECG
5) In cases of phrenic nerve palsy at the Index Procedure, subjects should be re-assessed per center standard of care
6) Provide subjects with arrhythmia/event monitor and operating instructions
7) New, discontinued or changes in study-collected medication information (e.g. AAD and NOAC)
8) Perform Cardiac CT/MRI if PV stenosis is suspected at any time throughout the follow-up period
9) NIHSS must be conducted by a person certified in the administration of the NIHSS between Day 1 and Day 7 post index procedure
   - If the NIH stroke scale demonstrates new abnormal findings when compared with the pre-procedure assessment, the subject will have a neurology consultation. A brain DW-MRI scan is required if neurology consultation determines possibility of new cerebral ischemic event. The DW MRI scan sequences required must be performed within the local guidelines associated with brain MRI scan. The following parameters for the DW-MRI are recommended in order to allow comparability of potential findings across patients:
     a) 1.5T MRI imaging equipment
     b) Diffusion-weighted imaging technique
     c) 5mm slice thickness
10) Reportable Adverse Events, if applicable
11) Protocol Deviations, if applicable

10.6.4. **One Month Follow-Up Visit (30 days +/-10 days)**

The 1-Month Follow-up Visit must occur within 30 ± 10 days post Index Procedure.

The data collection at the 1-Month Follow-up Visit includes:

1) Date of visit
2) Cardiovascular/Pulmonary Exam at discharge must be completed by a someone qualified to perform the physical assessment i.e. physician/medical doctor, nurse practitioner (NP) and/or Physician Assistant (PA) and include:
   - Lung auscultation (includes respiratory rate and respiratory rhythm)
   - Heart auscultation
3) Physical assessment performed as standard of care including temperature, O_2 saturation, weight, resting heart rate, systolic and diastolic blood pressure
4) Rhythm at time of visit by means of a 12-lead ECG
5) Review of any symptomatic transmissions from event monitor
   a. Review expectations for arrythmia/event monitor transmissions with subjects
6) Documentation of any intervention for AF/AT/AFL (e.g. Repeat Procedure, Cardioversion), if applicable
7) Subjects with unresolved phrenic nerve palsy detected at the discharge visit must be re-assessed per center's standard of care to evaluate if the event resolved
8) Perform Cardiac CT/MRI if PV stenosis is suspected at any time throughout the follow-up period
9) New, discontinued or changes in study-collected medication information (e.g. AAD and NOAC)
10) Reportable Adverse Events, including resolution of ongoing events, if applicable
11) Protocol Deviations, if applicable

10.6.5. **Three Month Follow-Up Visit (91 days +/-14 days)**

The 3-month Follow-up Visit must occur within 91 ±14 days post Index Procedure.

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

1) Date of visit
2) Quality of Life Instruments (AFEQT and EQ-5D-5L). It is highly recommended that these assessments be completed prior to the remaining clinical assessments (e.g., 12-lead ECG and physical assessment).
3) Physical assessment performed as standard of care including temperature, O_2 saturation, weight, resting heart rate, systolic and diastolic blood pressure
4) Rhythm at time of visit by means of a 12-lead ECG

5) Review of any symptomatic transmissions from event monitor that occurred prior to 3-month visit and
   - Review expectations for arrythmia/event monitor transmissions with subjects (e.g. subjects are required to submit their heart rhythms, symptomatic and asymptomatic, a minimum of twice per month)
6) Documentation of any intervention for AF/AT/AFL (e.g. Repeat Procedure, Cardioversion), if applicable
7) Subjects with unresolved phrenic nerve palsy detected at the discharge visit must be re-assessed per center's standard of care to evaluate if the event resolved
8) Perform Cardiac CT/MRI if PV stenosis is suspected at any time throughout the follow-up period
9) New, discontinued or changes in study-collected medication information (e.g. AAD and NOAC)
10) Reportable Adverse Events, including resolution of ongoing events, if applicable
11) Protocol Deviations, if applicable

10.6.6. **Six Month Follow-Up Visit (180 days +/-30 days)**

The 6-month Follow-up Visit must occur within 180 days ± 30 days post Index Procedure.

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

1) Date of visit
2) Quality of Life Instruments (AFEQT and EQ-5D-5L). It is highly recommended that these assessments be completed prior to the remaining clinical assessments (e.g., 12-lead ECG and physical assessment).
3) Physical assessment performed as standard of care including temperature, O_2 saturation, weight, resting heart rate, systolic and diastolic blood pressure
4) Rhythm at time of visit by means of a 12-lead ECG
5) Collection and review of any symptomatic or asymptomatic events from event monitor
   - Review expectations for arrythmia/event monitor transmissions with subjects (e.g. subjects are required to submit their heart rhythms, symptomatic and asymptomatic, a minimum of twice per month)
6) Apply the 24-hour Holter monitor on the subject and instruct subject to submit their heart rhythm
7) Documentation of any intervention for AF/AT/AFL (e.g. Repeat Procedure, Cardioversion), if applicable
8) Perform Cardiac CT/MRI if PV stenosis is suspected at any time throughout the follow-up period

9) Subjects with unresolved phrenic nerve palsy detected at the discharge visit must be re-assessed per center's standard of care to evaluate if the event resolved
10) New, discontinued or changes in study-collected medication information (e.g. AAD and NOAC)
11) Reportable Adverse Events, including resolution of ongoing events, if applicable;
12) Protocol Deviations, if applicable

10.6.7. **Twelve Month Follow-Up Visit (365 days ± 30 days)**

The 12-month Follow-up Visit must occur within 365 days ± 30 days post Index Procedure.

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

1) Date of visit
2) Quality of Life Instruments (AFEQT and EQ-5D-5L). It is highly recommended that these assessments be completed prior to the remaining clinical assessments (e.g., 12-lead ECG and physical assessment).
3) Physical assessment performed as standard of care including temperature, O_2 saturation, weight, resting heart rate, systolic and diastolic blood pressure
4) Rhythm at time of visit by means of a 12-Lead ECG
5) Collection and review of any symptomatic or asymptomatic events (via event monitor and 24-hour Holter). If the subject did not apply the 24-hour Holter prior to the 12-month visit, please apply the 24-hour Holter to the subject during the visit and request the subject submit their heart rhythm and to return the 24-hour Holter monitor after the assessment is complete.
6) Documentation of any intervention for AF/AT/AFL (e.g.: Repeat Procedure, Cardioversion), if applicable
7) Perform Cardiac CT/MRI if PV stenosis is suspected at any time throughout the follow-up period
8) Subjects with unresolved phrenic nerve palsy detected at the discharge visit must be re-assessed per center's standard of care to evaluate if the event resolved
9) New, discontinued or changes in study-collected medication information (e.g. AAD and NOAC)
10) Reportable Adverse Events, including resolution of ongoing events, if applicable
11) Protocol Deviations, if applicable

10.6.8. **Unscheduled Visit**

An unscheduled follow-up visit is any subject visit triggered by subject symptoms indicative of complications that may be associated with the catheter ablation procedure or cardiac arrythmia requiring an in-office visit per physician discretion.

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 deemed necessary per investigator's discretion.

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

1) Date of visit
2) Physical assessment performed as standard of care and including temperature, O_2 saturation, weight, resting heart rate, systolic and diastolic blood pressure
3) Rhythm at time of visit by means of a 12-Lead ECG
4) Collection and review of any symptomatic or asymptomatic events from the event monitor
5) Documentation of any intervention for AF/AT/AFL (e.g.: Repeat Procedure, Cardioversion), if applicable
6) Perform Cardiac CT/MRI if PV stenosis is suspected at any time throughout the follow-up period
7) Subjects with unresolved phrenic nerve palsy detected at discharge visit, should be reassessed per center standard of care to evaluate if phrenic nerve palsy has resolved
8) New, discontinued or changes in study-collected medication information (e.g. AAD and NOAC)
9) Reportable Adverse Events, including resolution of ongoing events, if applicable
10) Protocol Deviations, if applicable

10.7. Additional/Repeat Procedure

One repeat ablation procedure for PAF is allowed within the blanking period only if considered medically necessary due to subject's intolerability of the PAF. An additional ablation procedure outside the blanking period is considered an effectiveness endpoint failure. The StablePoint Catheter System must be used for a repeat ablation procedure. In case an additional ablation procedure (including to but not limited to additional ablation procedures for PAF) occurs during the month 12 follow up period, the data of this procedure will be entered in the 'Additional Procedure' eCRF.

A repeat ablation procedure for PAF may be medically necessary in certain subjects after the index ablation procedure due to recurrences of PAF or other tachyarrhythmias requiring treatment. If a repeat ablation procedure is conducted, the Investigator must follow the

protocol as outlined in **Sections 10.4 (Medications), 10.5 (General Study Information) and 10.6.2.1 through 10.6.2.6,** which describes the initial 3D mapping, ablation technique, PVI validation, esophagus management and phrenic nerve assessment. After the repeat procedure, a neurology consult is only required if NIHSS scale worsens from the previous assessment. The NIHSS at Pre-Discharge must be performed Day 1 to 7 after the repeat procedure. All NIHSS assessments must be completed by a person certified in the administration of the NIHSS. Data collection requirements for the repeat procedure for PAF are the same as those for the Index Procedure for PAF.

If the StablePoint Catheter System is not used for a repeat procedure during the blanking period, it is considered a deviation and a study endpoint failure.

Subjects must follow the same anticoagulation requirements as defined for the index procedure in **Section 10.4.2** prior to proceeding with the repeat ablation procedure for PAF.

10.8. Product Return (Investigational Only)

After IntellaNav StablePoint™ Catheter removal from the subject, the catheter should be inspected by the investigational site staff, and if any abnormalities such as char or coagulum formation are noted on the catheter, it must be documented. IntellaNav StablePoint™ Catheters, sheaths and extension cables opened and/or used during the procedure must be returned to the sponsor, if the product is considered investigational in that region. Failure to return an investigational IntellaNav StablePoint™ Catheters and Cable will result in a protocol deviation. All other control ablation or diagnostic catheters may be disposed of per standard EP practice. All adverse experiences with a BSC product, including those commercially available, during the ablation procedure must be promptly reported to BSC and documented on the eCRF.

10.9. Study Completion/End of Study

Each TREATMENT subject will be followed until the 12 Month Follow-Up Visit is completed. The end of the study is defined as completion of the last visit shown in the Data Collection Schedule including the 12-month follow-up visit and 24-hour Holter Monitor. Attempt subjects will be followed up to the 30 day Follow-Up Visit. However, attempt subjects will not need to complete post-procedure arrythmia monitoring.

Even though a subject's participation in the clinical study has ended, physicians may wish to continue standard of care visits outside of the study.

In case of premature termination of the study, please refer to **Section 9**. Following termination/completion of the study, subjects will be managed according to local institution practice.

Sites must to complete the "End of Study" CRF to signify study completion.

10.10. Unforeseen Circumstances (Natural Disaster/Global Pandemic)

There may be unforeseen circumstances that occur during the course of the study, such as a natural disaster (e.g. hurricanes, tornadoes) or a global pandemic (e.g. COVID-19) that prevents a subject from attending study visits during the required follow-up window. While every attempt should be made to avoid disruptions in collecting study data, it is important to collect as much data as possible, by any available means and from any available resources. This may include obtaining records from an outside clinic, hospital or other healthcare facility that is not IRB/EC approved.

In the event that study data must be collected remotely, every effort should be made to collect the data within the study visit window, if possible. Critical data collected during the study includes any procedure or device related adverse events, recurrence of any AF/AT/AFL, and a Cardiac CT or MRI (if PV stenosis is suspected). Event monitors and 24-hour Holter monitors can be used to detect any recurrence of AF/AT/AFL. If a Cardiac CT or MRI is required because PV stenosis is suspected, the Cardiac CT or MRI may be performed at another healthcare facility and the window to conduct this test may be extended by up to one month (30 days) following the normal study visit window. If the subject is not able to have his/her heart rhythm assessed via a 12-lead ECG, it will not be a protocol deviation.

10.11. Source Documents

Table 10-3 summarizes all source data requirements for this protocol. 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 10-3**.

Table 10-3: Source Documentation Requirements

Requirement	Disposition
Screening and Enrollment Log	Retain at Center
Informed consent documentation process and investigator eligibility assessment	Retain at Center
Medical history documents pertaining to eligibility criteria	Retain at Center
Documentation of demographics data	Retain at Center
Pregnancy test, if applicable	Retain at Center
Physical assessment	Retain at Center
Cardiovascular/pulmonary examination	Retain at Center
Medication Regimen and Changes	Retain at Center
Medical history	Retain at Center
Electrocardiographically documented episodes of Atrial Fibrillation can include, but is not limited to: • ECGs • TTE/TEE • Event Monitors • 24H Holters • Rhythm Strips – note that if the irregular heart rhythm was captured via a wearable, the Investigator must review the rhythm strip, document confirmation of Atrial Fibrillation and sign and date the printed rhythm strip. If the rhythm strip is not printed, documentation of Investigator review and confirmation of the atrial fibrillation must be located in the EMR system.	Retain at Center
Quality of Life Instruments (AFEQT and EQ-5D-5L)	Retain at Center
NIH Stroke Scale Assessments	Retain original at center and submit copies and all associated source documents if a change in scale is observed from baseline
Neurological Consultation, if applicable	Retain at Center
Imaging	Retain at Center
Labs	Retain at Center
12-Lead ECGs data including ongoing rhythm	Retain at Center and submit to core lab, if applicable
Recording System printouts showing entrance/exit block for each PV	Retain at Center
Recording lab logs, showing the time of entrance block at a minimum, and exit block if tested	Retain at Center
Signed Technical Source Form	Retain at Center
Rhythmia HDx™ Export Case Data	Final storage on external media Retain one copy at center and submit one to BSC
EP Lab Procedure Report	Retain at Center
Adverse Events	Retain at Center
In the event of a patient death: • Death narrative • Relevant medical records • Death Certificate • Autopsy report Events be adjudicated by CEC: Relevant medical records	Submit one copy to BSC, Retain one copy at center

11. Statistical Considerations

11.1. Primary Endpoints

11.1.1. Primary Safety Endpoint at 30 Days

The primary safety endpoint at 30 days consists of acute primary safety endpoint events as defined in **Section 6.1**. This endpoint will be evaluated by the primary safety event-free rate at 30-days post-procedure, which will be assessed at the time of the 6-month analysis.

11.1.1.1. Hypotheses

The primary safety objective at 30 days is to demonstrate the primary safety event-free rate through 30-days post-procedure is greater than the specified performance goal.

- Ho: The primary safety endpoint event-free rate at 30-days post procedure $\leq 90\%$
- Ha: The primary safety endpoint event-free rate at 30-days post procedure $> 90\%$

11.1.1.2. 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 at 30 Days
Expected rate	95%
Performance goal	90%
Attrition (per year)	5%
Significance level (one-sided)	5%
Power	90%
Sample size	252

Under the hypothesis and assumptions outlined above, the required sample size for this endpoint is 252 subjects treated with the IntellaNav StablePoint Catheter.

The expected rate and performance goal for the primary safety endpoint at 30 days was determined by the meta-analysis below. The meta-analysis was inclusive of recent RF IDE studies, as well as the SMART-SF safety study. The rate of the 30-day primary safety endpoint events in each of the studies was determined and an overall rate was calculated using a random effects model. This overall rate was used to define the expected event rate for the endpoint. The performance goal was derived from the sum of the 95% upper confidence bound of the overall rate and a margin of indifference of 50% of the upper confidence bound. This resulted

in a 5% expected event rate (95% event-free rate) and 10% performance goal (90% event-free performance goal).

Meta-Analysis to Determine Expected Rate and 95% CI for 30 Day Primary Safety Endpoint at 30 Days					
Study	**Primary Endpoint Completion Year**	**Technology**	**Events/ Total**	**Rate (%)**	**95% CI**
TOCCASTAR	2013	RF - Tacticath	9/152	5.92	(2.74, 10.94)
TOCCASTAR	2013	RF - Control	7/143	4.90	(1.99, 9.83)
SMART-AF	2013	RF - SmartTouch	11/161	6.83	(3.46, 11.90)
HEARTLIGHT	2014	RF - Control	7/172	4.07	(1.65, 8.21)
SMART-SF	2015	RF – SmartTouch SF	4/159	2.52	(0.69, 6.32)
ZERO AF	2016	RF – Blazer OI	9/157	5.73	(2.65, 10.60)
ZERO AF	2016	RF - Control	5/164	3.05	(1.00, 6.97)
OVERALL*				**4.93**	**(3.77, 6.42)**
* Overall rate and 95% CI were calculated using a binary random effects model					

11.1.1.3. Statistical Methods

The 30-day primary safety event-free rate will be calculated using Kaplan-Meier methodology. Subjects who withdraw from the study prior to 30 days without experiencing an event will be censored on the date of their last study visit. The 95% one-sided lower confidence limit of the observed safety event-free rate at 30 days will be compared to the performance goal of 90%. 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.

11.1.2. **Primary Effectiveness Endpoint – Acute Procedural Success**

The primary effectiveness endpoint of acute procedural success is defined as a subject that successfully had confirmed pulmonary vein isolation, by demonstration of entrance block at a minimum and no evidence of exit conduction with the study catheter only. This endpoint will be assessed at the time of the 6-month analysis.

11.1.2.1. Hypotheses

The primary effectiveness objective for acute procedural success is to demonstrate that the acute procedural success rate is greater than the specified performance goal.

- Ho: The acute procedural success rate procedure ≤ 92%
- Ha: The acute procedural success rate > 92%

11.1.2.2. Sample Size

The sample size estimate was calculated employing exact binomial methodology. The following assumptions were used in the sample size calculation:

Assumptions	Acute Procedural Success
Expected rate	98%
Performance goal	92%
Attrition (per year)	0%
Significance level (one-sided)	2.5%
Power	90%
Sample size	160

Under the hypothesis and assumptions outlined above, the required sample size for this endpoint is 160 subjects treated with the IntellaNav StablePoint Catheter.

The expected rate for the primary effectiveness endpoint of acute success was based on the acute effectiveness rate for the BOI catheter observed in the ZERO AF clinical study. The SMART-SF also had an acute procedural success effectiveness primary endpoint and observed a success rate of 96.2% (95% CI: 92%, 98.6%). As the effectiveness endpoint was passed in this study, the lower confidence limit of 92% was assumed to be an acceptable level of acute procedural effectiveness and was used as a performance goal for the primary effectiveness endpoint of acute procedural success.

11.1.2.3. Statistical Methods

The 97.5% one-sided Clopper-Pearson lower confidence limit of the observed acute procedural success rate will be calculated. If the lower confidence limit is greater than the performance goal of 92%, the null hypothesis will be rejected.

11.1.3. Primary Effectiveness Endpoint at 6 Months

The primary effectiveness endpoint at 6 months consists of endpoint events as defined in **Section 6.3**. The primary effectiveness endpoint at 6 months will be assessed at the 6-month analysis. If this analysis fails to reject the null hypothesis, primary effectiveness may be reevaluated at 12 months post-procedure via the primary effectiveness endpoint at 12 months.

11.1.3.1. Hypotheses

The primary effectiveness objective at 6 months is to demonstrate that the primary effectiveness event-free rate through 6 months post-procedure is greater than the specified performance goal:

- Ho: The 6-month primary effectiveness event-free rate $\leq 60\%$
- Ha: The 6-month primary effectiveness event-free rate $> 60\%$

11.1.3.2. 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	Primary Effectiveness at 6 Months
Expected rate	72%
Performance goal	60%
Attrition (per year)	10%
Significance level (one-sided)	2.5%
Power	90%
Sample size	183

Under the hypothesis and assumptions outlined above, the required sample size for this endpoint analysis is 183 subjects treated with the IntellaNav StablePoint Catheter.

The expected rate for the primary effectiveness endpoint at 6 months was determined based on Boston Scientific's ZERO AF study data. The performance goal was determined by the meta-analysis below. The meta-analysis was inclusive of recent RF IDE studies. The six-month primary effectiveness event-free rate was extracted from published Kaplan-Meier plots. All studies included only symptomatic events in their endpoint definition. Because both asymptomatic and symptomatic events will be counted towards the endpoint in the

NEwTON AF study (per the 2017 HRS Consensus Document), the following adjustment was made:

- Six-month primary effectiveness event-free rate in BSC ZERO AF data was calculated with and without asymptomatic events
- Percent reduction in primary effectiveness event-free rate with asymptomatic events added was calculated (2.9%)
- Reduction applied to other studies in meta-analysis to estimate primary effectiveness event-free rate including asymptomatic events

An overall primary effectiveness event-free rate at 6 months and two-sided 95% confidence interval were calculated using a random effects model. The performance goal was derived from the sum of the 95% upper confidence bound of the overall event rate and a margin of indifference of 50% of the upper confidence bound. This resulted in a 24% expected event rate (76% event-free rate) and 40% performance goal (60% event-free performance goal).

Meta-Analysis to Determine Performance Goal for Primary Effectiveness Endpoint at 6 Months					
Study	**Primary Endpoint Completion Year**	**Technology**	**N**	**6M Event Free Rate (Study Definition)**	**6M Event Free Rate Including Asymptomatic Events***
TOCCASTAR	2013	RF - Tacticath	146	79.5%	77.2%
TOCCASTAR	2013	RF - Control	134	79.8%	77.4%
SMART-AF	2013	RF - SmartTouch	122	81.4%	79.0%
HEARTLIGHT	2014	RF - Control	167	77.4%	75.2%
ZERO AF	2016	RF – Blazer OI	157	72.9%	71.6%
ZERO AF	2016	RF - Control	164	79.1%	76.0%
OVERALL**					**76% (73%, 79%)**
*using percent reduction in event free rate with asymptomatic events from ZERO AF, where applicable					
** Overall rate and 95% CI were calculated using a binary random effects model					

11.1.3.3. Statistical Methods

For the analysis of the primary effectiveness endpoint at 6 months, the Kaplan-Meier 6 month (183-day) primary effectiveness event-free rate will be calculated using all available data at the time of the 6-month analysis. This analysis will take place when 299 TREATMENT subjects have been enrolled and completed their 30-Day follow-up and 183 TREATMENT subjects have completed their 6-month follow-up. Event-free subjects who withdraw from the study or die prior 6 months due to a device or procedure related adverse event will be considered to have an endpoint event at the time of study exit. Subjects who withdraw from the study or die prior to 6 months without experiencing an event, as well as event-free subjects who are still active in the study at the time of the 6-month analysis

snapshot, will be censored on the date of their last study visit or arrhythmia/event monitor use, whichever is later. The 97.5% one-sided lower confidence limit of the observed 6-month primary effectiveness event-free rate will be compared to the performance goal of 60%. The lower confidence limit will be calculated as the pointwise confidence limit using the log-log methodology. If the lower confidence limit is greater than the performance goal, the null hypothesis will be rejected.

11.1.4. **Primary Safety Endpoint at 12 Months**

The primary safety endpoint at 12 months consists of a composite of acute and chronic safety endpoint events as defined in **Section 6.4**. The primary safety endpoint at 12 months will be evaluated by the primary safety event-free rate at 12 months post-procedure, which will be assessed after study completion.

11.1.4.1. Hypotheses

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

- Ho: The primary safety endpoint event-free rate at 12 months post procedure $\leq 89\%$
- Ha: The primary safety endpoint event-free rate at 12 months post procedure $> 89\%$

11.1.4.2. 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 at 12 Months**
Expected rate	94%
Performance goal	89%
Attrition (per year)	10%
Significance level (one-sided)	2.5%
Power	80%
Sample size	299

Under the hypothesis and assumptions outlined above, the required sample size for this endpoint is 299 subjects treated with the IntellaNav StablePoint Catheter. This analysis drives the overall sample size for the NEwTON AF study.

The expected rate and performance goal for the primary safety endpoint at 12 months were determined using the meta-analysis outlined in **Section 11.1.1** above and accounting for a 1% rate of safety events occurring between 30 days and 12 months.

11.1.4.3. Statistical Methods

The 12-month primary safety event-free rate will be calculated using Kaplan-Meier methodology. Subjects who withdraw from the study prior to 12 months without experiencing an event will be censored on the date of their last study visit. The 97.5% one-sided lower confidence limit of the observed safety event-free rate at 12 months will be compared to the performance goal of 89%. 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.

11.1.5. **Primary Effectiveness Endpoint at 12 Months**

The primary effectiveness endpoint at 12 months consists of endpoint events as defined in **Section 6.5**. The primary safety endpoint at 12 months will be evaluated by the primary safety event-free rate at 12 months post-procedure, which will be assessed after study completion.

11.1.5.1. Hypotheses

The primary effectiveness objective at 12 months will evaluate the primary effectiveness event-free rate through 12 months post procedure with the objective of demonstrating that this rate is greater than the pre-specified performance goal:

- Ho: The 12-month primary effectiveness event-free rate $\leq$ 50%
- Ha: The 12-month primary effectiveness event-free rate > 50%

11.1.5.2. 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 at 12 Months**
Expected rate	60%
Performance goal	50%
Attrition (per year)	10%
Significance level (one-sided)	2.5%

Power	90%
Sample size	288

Under the hypothesis and assumptions outlined above, the required sample size for this endpoint analysis is 288 subjects treated with the IntellaNav StablePoint Catheter.

The expected rate for the primary effectiveness endpoint at 12 months was determined based on Boston Scientific's ZERO AF study data. The performance goal for the primary effectiveness endpoint at 12 months is the 2017 HRS Consensus Document recommended performance goal.

11.1.5.3. Statistical Methods

For the analysis of the primary effectiveness endpoint at 12 months, the Kaplan-Meier (KM) 12-month (365-day) primary effectiveness event-free rate will be calculated. Event-free subjects who withdraw from the study or die prior to 12 months due to a device or procedure related adverse event will be considered to have an endpoint event at the time of study exit. Subjects who withdraw from the study or die prior to 12 months without experiencing an event will be censored on the date of their last study visit or arrhythmia/event monitor use, whichever is later. The 97.5% one-sided lower confidence limit of the observed 12-month primary effectiveness event-free rate will be compared to the performance goal of 50%. The lower confidence limit will be calculated as the pointwise confidence limit using the log-log methodology. If the lower confidence limit is greater than the performance goal, the null hypothesis will be rejected.

11.2. Secondary Endpoints

Secondary endpoint analyses will be performed after study completion and will be exploratory in nature. These endpoints have no powered hypotheses, and no alpha adjustment for multiple testing will be made.

11.2.1. **Secondary Safety Endpoint: SAE and AE Rates**

The secondary safety endpoint will evaluate the rate of Serious Adverse Events (SAE) and Adverse Events (AE) related to the procedure and/or study device through 12 months post Index Procedure.

11.2.2. **Secondary Effectiveness Endpoint 1: New or Increased Dose of AAD**

The first secondary effectiveness endpoint will evaluate the 12-month effectiveness rate when considering only newly prescribed or increased dosages of previously prescribed AADs as endpoint failures.

For this analysis endpoint events will be defined as:

- Acute procedural failure
- Use of non-study ablation catheter in the index procedure or in a repeat procedure during the blanking period
- 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 between 91 days and 365 days post index procedure captured by one of the following methods:
  - ≥ 30 seconds in duration from the study specific event monitor or Holter Monitor
  - ≥ 10 seconds 12-lead Electrocardiography (ECG)
- 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
  - Electrical and/or pharmacological cardioversion
  - Prescribed a new AAD*
  - Prescribed an increased dose of a previously failed AAD*

*AADs for endpoint will consist of all Class I/III, including Amiodarone, and any Class II/IV medications taken for control of atrial fibrillation (AF)/Atrial tachycardia (AT)/Atrial flutter (AFL) recurrence.

11.2.3. **Secondary Effectiveness Endpoint 2: Single Procedure Success**

The second secondary effectiveness endpoint will evaluate the 12-month effectiveness rate when considering only subjects who do not require a repeat procedure within the blanking period as a success.

For this analysis endpoint events will be defined as:

- Acute procedural failure
- A repeat procedure during the blanking period (90 days post index procedure)
- Documented atrial fibrillation, or new onset of atrial flutter or atrial tachycardia between 91 days and 183* days post index procedure captured by one of the following methods:
  - ≥ 30 seconds in duration from the study specific event monitor or Holter Monitor
  - ≥ 10 seconds 12-lead Electrocardiography (ECG)

- 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
    - Electrical and/or pharmacological cardioversion
    - Prescribed any AAD*

*AADs for endpoint will consist of all Class I/III, including Amiodarone, and any Class II/IV medications taken for control of atrial fibrillation (AF)/Atrial tachycardia (AT)/Atrial flutter (AFL) recurrence.

11.2.4. **Secondary Effectiveness Endpoint 3: Symptomatic Recurrence**

The third secondary effectiveness endpoint will evaluate the 12-month effectiveness rate when considering only documented symptomatic arrhythmia recurrences or interventions for arrhythmias as endpoint failures.

For this analysis endpoint events will be defined as:

- Acute procedural failure
- Use of non-study ablation catheter in the index procedure or in a repeat procedure during the blanking period
- More than one repeat procedure during the blanking period (90 days post index procedure)
- Documented symptomatic atrial fibrillation, or new onset of symptomatic atrial flutter or symptomatic atrial tachycardia between 91 days and 365 days post index procedure captured by one of the following methods:
    - $\geq$ 30 seconds in duration from the study specific event monitor or Holter Monitor
    - $\geq$ 10 seconds 12-lead Electrocardiography (ECG)
- 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
    - Electrical and/or pharmacological cardioversion
    - Prescribed any AAD*

*AADs for endpoint will consist of all Class I/III, including Amiodarone, and any Class II/IV medications taken for control of atrial fibrillation (AF)/Atrial tachycardia (AT)/Atrial flutter (AFL) recurrence.

11.3. General Statistical Methods

11.3.1. Analysis Sets

While each endpoint was individually powered, each safety endpoint analysis will use all available data from all ATTEMPT and TREATMENT subjects, and each effectiveness endpoint analysis will use all available data from all TREATMENT subjects.

11.3.2. Control of Systematic Error/Bias

11.3.2.1. Control of Potential Bias

Selection of patients will be made from the Investigator's population. All patients meeting the eligibility criteria and having signed the ICF will be eligible for enrollment in the study. Control and reduction of potential bias associated with a single-arm study design have been taken into account by considering a series of measures including but not limited to:

- defining inclusion and exclusion criteria to represent a population similar to the one enrolled in recently completed trials on AF ablation;
- employing a rhythm surveillance monitoring strategy that is equivalent to that used in recent PAF IDE studies and consistent with the relevant recommendation in the HRS consensus document;
- utilizing core lab for reviewing electrocardiographic recordings from study specific rhythm surveillance monitoring after the blanking period.

11.3.2.2. Control of Type I Error

Either of the primary effectiveness endpoints at 6 or 12 months must be met to achieve study success for PMA submission. Since each of these endpoints is tested at a one-sided significance level of 0.025, the family-wise type I error across both endpoints is maintained below 0.05. The primary safety endpoint at 30 days and the primary effectiveness endpoint for acute procedural success must also be met to achieve study success for PMA submission, and both endpoints will be tested at a one-sided significance level $\leq$0.05. Therefore, following the methodology of the Intersection-Union Test (IUT), the overall type I error across the study success for PMA submission criteria will be maintained below 0.05.

The criteria for overall study success are the same as that for study success for PMA submission, with the added conditions that the primary safety and effectiveness endpoints at 12 months must be met. Since both endpoints will be tested at a one-sided significance level of 0.025, the overall type I error across the overall study success criteria will be maintained below 0.05.

11.3.3. Number of Subjects per Investigative Site

To avoid any center effect and bias, enrollment controls will be implemented to ensure no study site will be allowed to contribute more than 15% for the first 183 TREATMENT subjects (27 subjects/center) and then once 183 subjects are enrolled, no more than 15% of the remaining subject enrollment (44 subjects/center) of the total required enrollment.

11.4. Data Analyses

11.4.1. Six Month Analyses

A 6-month endpoint analysis is planned and will be conducted after all 299 TREATMENT subjects have completed 30 days of follow up and 183 TREATMENT subjects have completed their 6-month follow-up.

11.4.2. 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)
- Geography (International vs. United States)

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.

In addition to subgroup analyses, descriptive statistics of subject demographic and baseline characteristics will be presented for each subgroup listed in this section.

11.4.3. Justification of Pooling

Center-to-center heterogeneity will be assessed for the primary endpoints by performing a Chi-square test, treating site as a fixed effect. Descriptive statistics for each site will be presented but small sites (sites enrolling less than five subjects) will be excluded from the poolability analysis. If sites are not deemed poolable in the initial Chi-square analysis, the poolability analysis will be reperformed by treating site as a random effect. A significance level of 15% will be used for each test.

11.4.4. Multivariable Analyses

For each primary endpoint, univariate analyses of the following covariates will be performed, and any found to be significantly associated with the outcome at the 0.15 alpha level will be included as covariates in a multivariate regression model. Backward selection with 0.15 alpha level stay criterion will be used to determine the final multivariate model.

The list of baseline covariates includes, but is not necessarily limited to:

- Subject demographics (e.g. age, gender)
- Subject baseline characteristics (e.g. LVEF and LA diameter, cardiovascular disease histories and disease types)
- Procedural techniques (e.g., esophageal temperature monitoring)

11.4.5. **Additional Analyses**

Other additional endpoints and analysis include, but are not limited to:

- Changes in the quality of life measures (AFEQT and EQ-5D-5L) between baseline and 12 months follow up
- Total RF time for the index procedure (defined as the summation of all RF application durations)
- Total number of RF applications
- Total fluoroscopy time for the index procedure
- Total index procedure time
- Freedom from recurrence of individual types of atrial arrhythmias between 91 and 365 days from index procedure: 1) AF 2) AT 3) AFL
- Freedom from cardiovascular hospitalization at 12 months
- Quantification of parameters used during RF Application including RF power, RF duration, contact force and Local Impedance via DIRECTSENSE™ technology
- Descriptive summaries of primary safety and effectiveness endpoints at 12 months using the data available at the time of the 6-month analysis
- The predicted probability of success for the primary effectiveness endpoint at 12 months based off the data available at the time of the 6-month analysis.

Additional information on these analyses is included in the Statistical Analysis Plan.

11.4.6. **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.

12. Health Economics Outcomes

A formal health economics analysis may be completed as part of this trial study, given meaningful clinical results are obtained. This will take into consideration complication rates, quality of life, and resource utilization. The EQ-5D-5L, generic quality of life measure, will be used to assess health utilities. We may estimate costs associated with the health care utilization measures at all sites. These inputs may be used in health economics analysis performed.

13. Data Management

13.1. 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 databases used in this clinical study have been designed to meet regulatory compliance for deployment as part of a validated system compliant with laws and regulations applicable and to the conduct of clinical studies pertaining to the use of electronic records and signatures. Database backups will be 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 will also be provided only 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.

Data transfers from other systems such as the Rhythmia HDx System or core labs will be coordinated by Boston Scientific.

All access to the clinical database will be changed to "Read only" after all data is either "Hard Locked" or "Entry Locked". Once acceptance of the final report or finalization of publications (as applicable) is received, final database storage and archiving activities can begin. Once all the closeout activities are completed a request to IT is submitted to have the "Database Locked" or Decommissioned and all database access revoked.

13.2. 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.

13.3. Technical Source Forms

The Boston Scientific study team will create a Technical Source Form (TSF) to capture protocol required data elements that are not located in any other source documents. The TSF will be provided to the study sites for use as a source document. The protocol trained Boston Scientific representative may only use study-specific TSFs provided and approved by the Boston Scientific study team. Data collected on any site created worksheets must not be attributable to the Boston Scientific representative. The Boston Scientific representative providing technical support is not part of the site study team.

General TSF documentation considerations for the protocol trained Boston Scientific representative are as follows:

- Data that is collected as part of a clinical study must be attributable to the individual collecting/providing the data, and must include the individual's name, signature, and date of signature.
- Boston Scientific Representative involvement with data collection/providing source documentation should be minimized.
- Any source data collected to capture protocol required data elements by a Boston Scientific representative must be provided to a member of the study team at the conclusion of the visit and retained at the site.
- The Boston Scientific representative and Research Coordinator must make arrangements in advance as to how the clinical trial data will be transferred from the Boston Scientific representative to a member of the study team.
- The Boston Scientific representative completes the sections of the TSF that are appropriate to his/her role only (e.g., technical sections.)
- The Boston Scientific representative signs and dates completed sections of the TSF applicable to the Boston Scientific representative role. The Boston Scientific representative may assist in obtaining the signature and date of the Investigator or clinical research site staff delegated by the Investigator to oversee the study activity.

Collection and completion of all information on the TSF is the responsibility of the appropriate personnel as defined on the TSF. If available, the protocol trained Rhythmia mapping specialist or other protocol trained Boston Scientific representative will provide the delegated site personnel with the study related data collected during the case directly from the Rhythmia HDx™ system.

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

- Delegated Site Personnel completing the forms
- Delegated Investigator conducting and/or supervising the case
- BSC personnel supporting the visit

13.4. Core Laboratories

13.4.1. Event Monitors

A Core Lab will provide the center with all necessary instructions and/or materials related to the use of the event monitor. It is the responsibility of the site personnel/center to educate the subject on how to use the event monitor. If the subject is unable to submit their heart rhythms, core lab personnel may contact the subject to troubleshoot any issues with the event monitor. Only TREATMENT subjects will be provided with an event monitor. The event monitor will be provided to the subject prior to discharge from the hospital or at the 1-month visit. All events will be analyzed by the centralized research company to determine if the episodes are associated with arrhythmia recurrence. The Core Lab will make this information accessible to the Investigator center for concurrence. The third-party cardiologist will be used for final rhythm determination and final adjudication of the event.

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/or treatment of early recurrences. After the subject's 3-month follow-up visit, subjects will be instructed to send at least two transmissions per month (either symptomatic or asymptomatic) through the 12-month follow-up to ensure continued reporting compliance. If subjects experience symptoms associated with cardiac arrhythmias (e.g. palpitations, lightheadedness, syncope, dyspnea), they will be instructed to transmit a recording. Such recordings will count towards the required transmission of that period. The Core Lab will work with the investigational site to ensure reporting compliance.

All event monitors should be returned to the Core Lab or the Sponsor upon completion of a subject's 12-month follow-up or withdrawal from the study.

13.4.2. 24-Hour Holter Monitors

All TREATMENT subjects will be provided with 24-hour Holter Monitors at the 6-month follow-up visit and the 12-month follow-up visit. Subjects must return the 24-hour Holter to the site shortly after the 6-month follow-up visit and shortly after the 12-month follow-up visit. The site will send the 24-hour Holter Monitor data to the third-party reviewer; failure to do so will result in a protocol deviation.

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 , the monitor will be analyzed for all symptomatic and asymptomatic arrhythmia episodes, and investigators will be informed of the results.

13.4.3. ECG Core Lab

To ensure objective assessment of rhythm monitoring data, 12-lead ECG tracings obtained beyond 3 months post-procedure will be reviewed by an independent core lab for any TREATMENT subject.

ECGs obtained on subjects who undergo a repeat ablation outside of the blanking period will not be required to be reviewed by an independent core lab.

13.4.4. **Quality of Life (QOL)**

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.

The EQ-5D-5L, 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-5L dimension.

Both QOL assessments require IRB/EC approval prior to use within the study.

14. 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, and the regulatory authority if applicable 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 5 working days after the emergency occurred, or per prevailing local requirements, if sooner than 5 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 an eCRF. Sites may also be required to report deviations to the IRB/EC/REB, and the regulatory authority, per local guidelines and national/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. The sponsor will not approve protocol waivers.

15. Device/Equipment Accountability for Products Labelled Investigational

In geographies where the StablePoint Catheter System is considered investigational, the investigational devices/equipment shall be securely maintained, controlled, and used only in this clinical study. An electronic database or paper device accountability records will be used to track subjects and device allocations during the study. Investigational equipment shall be returned in the condition in which it was provided, reasonable wear and tear excepted.

For investigational-labelled items, the principal investigator or an authorized designee shall do the following:

- Securely maintain and control access to these items to ensure they are used only in this clinical study and only per the protocol.
- Ensure the storage environment for these items is appropriate for maintaining conditions per the items' labeling (e.g. temperature, humidity, etc., as applicable)
- Return remaining items upon Sponsor request and in the condition in which they were provided, reasonable wear and tear excepted

The sponsor shall keep records to document the physical location of all investigational devices/ equipment from shipment of investigational devices from BSC or designated facility/equipment to the investigation sites until return or disposal.

Records shall be kept by the investigational site to document the physical location and conditions of storage of all investigational devices/equipment.

The principal investigator or an authorized designee shall maintain accurate and timely Device Accountability Records documenting the receipt, use, return and disposal of the investigational devices/equipment, which shall include the following

- Maintain accurate and timely Device Accountability Records, providing copies to Sponsor upon request. Such records shall include the following content, at minimum:
  - Name(s) of person(s) who received, used, returned, or disposed of each item;
  - Date of receipt;
  - Identification and quantity of each item (examples of identification: batch number, serial number or unique code);
  - Expiry date for each item (or batch of items), as applicable;
  - Date or dates of use;
  - Subject identification;
  - Date on which the item was returned/explanted from subject, if applicable;

- Date of return (and number) of unused, expired, no longer needed, and/or malfunctioning items, as applicable;
- Date and documentation of item disposal, as directed by sponsor, if applicable.

16. Compliance

16.1. Statement of Compliance

This clinical investigation is financed by the study sponsor. Before the investigational site can be "Authorized to Enroll," the investigational site must enter into a Clinical Study Agreement with the sponsor that details the financing of the study as well as the rights and obligations of the investigational site and the investigator.

This study will be conducted in accordance with 21 CFR 814.20 part 56, part 50 and part 812 or 813, 45 CFR part 46, ISO 14155: Clinical Investigation of Medical Devices for Human Subjects - Good Clinical Practice, 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.

16.2. 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, 21 CFR 814.20 part 56, part 50 and part 812 or 813, ISO 14155: Clinical Investigation of Medical Devices for Human Subjects - Good Clinical Practice, 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.
- Prior to beginning the study, sign the Investigator Brochure Signature Page, if applicable, and the Protocol Signature page, documenting his/her agreement to conduct the study in accordance with the protocol.
- 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 reportable events
- 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.
- Maintain the device accountability records and control of the investigational device, ensuring that the investigational device is used only by authorized/designated users and in accordance with this protocol and instructions/directions for use.
- 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 investigational 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.

All investigators will provide their qualifications and experience to assume responsibility for their delegated tasks 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.

16.2.1. **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 to ensure study staff are competent to perform the tasks they have been delegated and provides 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 investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

16.3. Institutional Review Board/ Ethics Committee/ Research Ethics Board

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 ICF, must be received by the sponsor before recruitment of subjects into the study and shipment of investigational product/equipment. 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.

16.4. Sponsor Responsibilities

The NEwTON AF Study is sponsored by Boston Scientific Corporation. Boston Scientific (Sponsor) has conducted many global clinical trials. Boston Scientific is dedicated to transforming lives through innovative medical solutions that improve the health of patients around the world. 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.

16.4.1. 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 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 (including the StablePoint Catheter System and other support equipment).

At the request of the investigator and while under investigator supervision, trained BSC personnel may operate equipment during ablation procedure, assist with the conduct of testing specified in the protocol, and interact with the subject to accomplish requested activities. Typical tasks may include the following:

- Setting up, calibrating and/or operating parameters to investigator-requested settings of the StablePoint Catheter System 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 and interpretation of information contained therein to support the collection of required information by the delegated site staff.

- Print out reports directly from the System and provide original to clinical site as source documentation.
- Provide technical expertise/support to subjects during office visits and/or during teleconference calls/electronic communications with the principal investigator or their delegated site staff and the subject.
- Assisting with the collection of study data from the Rhythmia HDx Mapping System and other equipment, including assisting the site with uploading data exports from the System
- Entering technical data on technical source form as long as the responsible investigator verifies and signs the completed form

In addition, BSC personnel may perform certain activities to ensure study quality. These activities may include the following:

- Observing testing or medical procedures to provide information relevant to clinical protocol compliance
- Reviewing collected data and study documentation for completeness and accuracy

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
- Independently collect critical study data (defined as primary or secondary endpoint data) without review and approval of the investigator
- Enter data in electronic data capture systems or on paper case report forms

16.5. Insurance

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

17. Monitoring

Monitoring will be performed during the study to assess continued compliance with the protocol and applicable regulations. 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 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 remote or on-site monitoring visits or audits and that sufficient time is devoted to the process.

18. Potential Risks and Benefits

18.1. Anticipated Adverse Events

Subjects participating in this study are subject to the same risks shared by all subjects undergoing an ablation procedure for treatment of PAF. Since the handling and shaft characteristics of the investigational catheter are designed to be similar to those of other approved catheters for AF ablation, it is anticipated that the rate of catheter-related complications in this study will be similar to those reported from catheter ablations performed with approved catheter ablation systems. The protocol-required testing for this study uses standard techniques that are routinely used for the treatment and management of subjects with drug refractory PAF.

Based upon the current literature and BSC reports on adverse events with an ablation catheter, the Table below includes a list of the possible anticipated adverse events and possible adverse device effects associated with ablation with an ablation catheter for the treatment of PAF. Occurrence of any of the listed events could lead to prolonged hospitalization for the subject.

The following anticipated adverse events (AE) and adverse device effects (ADE) have been identified for this study. (**Table 18-1**)

Table 18-1: Potential Adverse Events and Adverse Device Effects for PAF ablation and Study Device

Pain or discomfort, for example: • Angina • Chest pain • Non-cardiovascular pain
Cardiac arrest
Death
Hypertension
Hypotension
Infection/inflammation/exposure to biohazardous material
Edema/heart failure/ pleural effusion

Procedural related side effects, for example: • Allergic reaction (including anaphylaxis) • Genitourinary complication • Side effects related to medication or anesthesia • Radiation injury/tissue burn • Renal failure/insufficiency • Vasovagal response
Respiratory arrest/distress/insufficiency/dyspnea

• Arrhythmia (new or exacerbated)
• Conduction pathway injury (Complete heart block (transient or permanent), nodal injury, etc.)
• Nerve injury, for example:
  ○ Phrenic nerve injury
  ○ Vagal nerve injury
• Gastrointestinal disorders
• Vessel trauma, including:
  ○ Perforation
  ○ Dissection
  ○ Coronary artery injury
  ○ Vasospasm
  ○ Occlusion
  ○ Hemothorax
• Cardiac trauma, for example:
  ○ Cardiac perforation/cardiac tamponade/pericardial effusion
  ○ Valvular damage
  ○ Stiff left atrial syndrome
• Injury related to tissue damage and/or adjacent structures and/or related structures, for example:
  ○ Esophageal injury
  ○ Physical trauma
  ○ Pulmonary injury
  ○ Catheter Entrapment
• Fistula, for example:
  ○ Atrio-esophageal fistula
  ○ Bronchopericardial fistula
• PV stenosis and its symptoms, for example:
  ○ Cough
  ○ Shortness of breath,
  ○ Fatigue
  ○ Hemoptysis
• Surgical and access complications, for example:
  ○ Hematoma/seroma
  ○ AV fistula
  ○ Bleeding

○ Pseudoaneurysm ○ Pneumothorax ○ Residual atrial septal defect
Injury due to embolism/thromboembolism/air embolism/foreign body embolism • Cerebrovascular Accident (CVA)/stroke • Transient Ischemia Attack (TIA) • Myocardial infarction • Neurological impairment and its symptoms, for example: ○ Cognitive changes, visual disturbances, headache, motor impairment, sensory impairment, and speech impairment • Pulmonary embolism • Asymptomatic cerebral embolism

The potential adverse events may be related to the diagnostic mapping catheter(s) and/or the interventional ablation device(s) and/or the procedure. The severity and/or the frequency of these potential adverse events may vary and may result in prolonged procedure time and/or additional medical and/or surgical intervention, implantation or permanent device such as a pacemaker, and in rare cases, may result in death. Refer to the RF Controller, Irrigation Pump, and other ancillary device instructions for additional potential adverse events related to their use with the IntellaNav StablePoint.

18.2. Risks Associated with the Study Device(s)

Benchtop studies and Pre-clinical research have demonstrated that the System is safe for human use. All potential risks have been evaluated and mitigation strategies have been implemented to reduce potential risks to acceptable levels.

18.3. Risks associated with Participation in the Clinical Study

There are no specific tests outside of standard practice required by this clinical study protocol. Therefore, there is no foreseen increased risk to subjects for participating in the NEwTON AF Study.

18.4. Risk Minimization Actions

Additional risks may exist. Risks can be minimized through compliance with this protocol, using the devices in accordance with their applicable Directions for Use, performing the procedures following recommended standard practices/guidelines, 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.

18.5. Anticipated Benefits

Subjects may or may not receive any benefit from participating in this study as compared to the current standard of care received for treatment of PAF. Potential benefits of the StablePoint Catheter System for the subject may include the following:

- Complete or partial reduction in symptoms related to PAF
- Complete or partial reduction in the number of cardioversions, medications a subject is taking, and in the number of hospitalizations related to PAF

18.6. Risk to Benefit Rationale

Risk management activities, including Hazard Analyses (HA) and Failure Mode Effects Analyses (FMEA), have been performed on the IntellaNav StablePoint Catheter and Force Sensing 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.

19. Safety Reporting

19.1. 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 of **reportable events**:

- All Serious Adverse Events
- All IntellaNav StablePoint Catheter and Force Sensing System Device Related Adverse Events
- All AEs associated with BSC commercialized devices
- All Procedure Related AEs
- All Thromboembolic Events
- All Device Deficiencies related to the BSC study device
- Unanticipated Adverse Device Effects/Unanticipated Serious Adverse Device Effects previously not defined in the IFU and ICF
- New findings/updates in relation to already reported events

Whenever possible, the medical diagnosis should be reported as the Event Term instead of individual symptoms. If it is unclear if 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.

The following clinical events will not be considered adverse events for this clinical study:

- Pre-existing diseases or conditions (including AFib, AFl, AT) will not be reported as adverse events unless there has been a substantial increase in severity or frequency of the problem as compared to the subject's baseline which cannot be attributed to the expected progression of the disease or condition.
- Pre-planned hospitalizations at time of enrollment or for a pre-existing condition.
- AF episodes with medical intervention or hospitalization due to arrhythmia recurrence during the blanking period (Index Procedure to 3 Month Follow-Up).

Death should not be recorded as an AE, but it should be reflected as an outcome of one (1) specific SAE (see **Table 19-1** for AE definitions).

The Boston Scientific Medical Safety group will provide safety oversight by reviewing and classifying individual events reported to the sponsor. Routine aggregate safety reviews will be conducted to ensure subject safety.

If an additional ablation procedure is required, this additional ablation procedure should only be considered an Adverse Event if it is associated with subject worsening condition or a new diagnosis. The ablation would be considered a corrective action.

If the subject experiences a new or worsening arrhythmia between the index procedure and the end of study, and the investigator considers this Adverse Event to be study related, it needs to be reported. Refer to Investigator's Brochure or IFU as appropriate for the known risks associated with the study device(s).

Refer to **Section 18.2** for the known risks associated with the study device(s).

19.2. Definitions and Classification

Adverse event definitions are provided in **Table 19-1**. Administrative edits were made on the safety definitions from ISO 14155 and MEDDEV 2.7/3 for clarification purposes.

Table 19-1: Safety Definitions

Term	Definition
Adverse Event (AE) *Ref: ISO 14155*	Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other

Term	Definition
Ref: MEDDEV 2.7/3	persons, in the context of a clinical investigation whether or not related to the investigational medical device and whether or not anticipated or unanticipated **NOTE 1**: This includes events related to the investigational medical device or comparator. **NOTE 2**: This definition includes events related to the procedures involved. **NOTE 3**: For users or other persons, this definition is restricted to events related to the investigational medical device.
Adverse Device Effect (ADE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Adverse event related to the use of an investigational 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 investigational medical device. **NOTE 2**: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device. **NOTE 3**: This includes 'comparator' if the comparator is a medical device
Serious Adverse Event (SAE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Adverse event that led to any of the following: • death, • serious deterioration in the health of the subject, users or other persons as defined by either: • a life-threatening illness or injury, or • a permanent impairment of a body structure or a body function, including chronic diseases, or • in-patient hospitalization or prolongation of existing hospitalization, or • medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function • fetal distress, fetal death, or a congenital abnormality or birth defect including physical or mental impairment. **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.

Term	Definition
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 risk assessment. **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.
Serious Health Threat *Ref: ISO 14155*	Signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons. Note 1: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.
Device Deficiency *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	An inadequacy of a medical device related to its identity, quality, durability, reliability, usability, safety or performance. **NOTE 1**: Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling. **NOTE 2**: This definition includes device deficiencies related to the investigational medical device or the comparator.
The following definitions will be used for defining hospitalization or prolongation of hospitalization for SAE classification purposes:	
Hospitalizations	Hospitalization does not include: • emergency room visit that does not result in in-patient admission Note: although an emergency room visit does not itself meet the definition for hospitalization, it may meet other serious criteria (e.g. medical or surgical intervention to prevent permanent impairment or damage) • elective and pre-planned treatment/surgery for a pre-existing condition that is documented in the subject's record at the time of consent/enrollment • admission for social reasons and/or respite care in the absence of any deterioration in the subject's general condition (e.g. subject is homeless, caregiver relief) • pre-planned, protocol-specified admission related to the clinical study (e.g. procedure required by protocol)
Prolongation of hospitalization	In-patient admission to the hospital that is prolonged beyond the expected standard duration for the condition under treatment.

Term	Definition
	Note: new adverse events occurring during the hospitalization are evaluated to determine if they prolonged hospitalization or meet another SAE criteria.

19.3. Relationship to Study Device(s) and/or Study Procedure

The Investigator must assess the relationship of the reportable AE to the study devices, or study procedure. See criteria in **Table 19-2.**

Table 19-2: 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, comparator 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 investigational 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 investigational 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.
Possibly Related *Ref: MEDDEV 2.7/3*	The relationship with the use of the investigational device, or comparator, or the relationship with procedures 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 investigational device, comparator, or the relationship with procedures seems relevant and/or the event cannot be reasonably explained by another cause, but additional information may be obtained.
Causal Relationship *Ref: MEDDEV 2.7/3*	The serious event is associated with the investigational 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 investigational device use/application or procedures; - the event involves a body-site or organ that -the investigational device or procedures are applied to the investigational 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 investigational 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.

19.4. Investigator Reporting Requirements

The communication requirements for reporting to BSC are as shown in **Table 19-3**.

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:

NEWTONAF.Safety@bsci.com

Table 19-3: Investigator Reporting Requirements

Event Classification	Communication Method	Communication Timeline pre-market studies (MEDDEV 2.7/3: CLINICAL INVESTIGATIONS: SERIOUS ADVERSE EVENT REPORTING UNDER DIRECTIVES 90/385/EEC AND 93/42/EEC)
Unanticipated Adverse Device Effect / Unanticipated Serious Adverse Device Effect	Complete AE eCRF page with all available new and updated information.	• Within 1 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.	• At request of sponsor.

Event Classification	Communication Method	Communication Timeline pre-market studies (MEDDEV 2.7/3: CLINICAL INVESTIGATIONS: SERIOUS ADVERSE EVENT REPORTING UNDER DIRECTIVES 90/385/EEC AND 93/42/EEC)
Serious Adverse Event	Complete AE eCRF page with all available new and updated information.	• Within 3 calendar days of first becoming aware of the event or as per local/regional regulations. • Reporting required through the end of the study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• At request of sponsor
Serious Adverse Device Effects	Complete AE eCRF page with all available new and updated information.	• Within 3 calendar days of first becoming aware of the event or as per local/regional regulations. • Reporting required through the end of the study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• When documentation is available • At sponsor request.
Device Deficiencies (including but not limited to failures, malfunctions, and product nonconformities) Note: Any Investigational 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 3 calendar days of first becoming aware of the event. • Reporting required through the end of the 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 10 business days) after becoming aware of the information • Reporting required through Study Exit • At sponsor request
	Provide all relevant source documentation (de-identified/pseudonymized) for reported event.	

* Please note that pre-market studies are clinical studies with investigational devices or with medical devices that bear the regulatory approval and are not being used for the same approved indications.

19.5. Boston Scientific Device Deficiencies

All device deficiencies (including but not limited to failures, malfunctions, use errors, product nonconformities, and inadequacy in the information supplied by the manufacturer) associated with the study devices (IntellaNav StablePoint Ablation Catheter) will be documented and reported to BSC. IntellaNav StablePoint™ Catheters, sheaths and extension cables opened and/or used during the procedure must be returned to the sponsor, if the product is considered investigational in that region. Failure to return an investigational IntellaNav StablePoint™ Catheters and Cable will result in a protocol deviation. All other control ablation or diagnostic catheters may be disposed of per standard EP practice. Instructions for returning the study catheters will be provided in study training. 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 failures and malfunctions should also be documented in the subject's medical record.

Device deficiencies (including but not limited to failures, malfunctions, and product nonconformities) are not adverse events. However, a reportable event that results from a device failure or malfunction, would be recorded as an adverse event on the appropriate eCRF.

For Device Deficiencies, the investigator must assess and report if the device deficiency 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.

19.6. 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.

19.7. 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/REB must be notified of any deaths in accordance with that site's IRB/EC/REB 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 catheter, clinical investigation, procedure, or patient condition
- Whether or not the death was witnessed
- Whether the patient 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 sub-investigator signature and date

Also submit the following documentation:

- If the patient 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 patient 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)

The Clinical Events Committee (CEC) must review information regarding subject deaths.

20. Informed Consent

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

The obtaining and documentation of Informed Consent must be in accordance with 21 CFR Parts 814.20, 56, 50 and 812, ISO 14155: Clinical Investigation of Medical Devices for Human Subjects - Good Clinical Practice; as applicable the Japan Medical Device GCP; ethical principles that have their origins in the Declaration of Helsinki; applicable individual country laws and any applicable national regulations, 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,
- 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 under the applicable laws, rules, regulations and guidelines and by the investigator and/or an authorized designee responsible for conducting the informed consent process. 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 5 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.

21. Committees

21.1. Safety Monitoring Process

The BSC personnel from the Medical Safety and Safety Trial Operation Teams review safety data as it is reported by the sites throughout the duration of the study. During scheduled monitoring activities, clinical research monitors further support this review through their review of source document and other data information. The BSC Medical Safety and Safety Trial Operations team includes health care providers with expertise in Electrophysiology and with the necessary therapeutic and subject matter expertise to evaluate and classify the events into the categories outlined above.

21.2. Clinical Events Committee

A Clinical Events Committee (CEC) is an independent group of individuals with pertinent expertise that reviews and adjudicates the following events as reported by study investigators:

- All Deaths which may be related to the procedure or the device
- All Adverse Events included in the composite primary safety endpoint per **Section 6.1** of Protocol
- All Adverse Events that are potentially related to the procedure or any of the devices included in the StablePoint Catheter System
- All unanticipated device effects
- Other events at the discretion of BSC

Committee members will include practitioners of Electrophysiology (EP), and/ or Cardiology, as well as other experts with the necessary therapeutic and subject matter expertise to adjudicate the event categories outlined above. Independent experts may be contracted to provide assessments of events listed above, as needed. A complete description of CEC responsibilities, qualifications, membership, and committee procedures will be outlined in the CEC charter.

From the data submitted by the center, BSC will provide a report of events as part of the safety event dossier described below, which may include: gender, date of procedure and device information, date of death, age at death, immediate cause of death, subject classification (e.g., attempt, intent, treatment), Investigator death classifications and death letter if provided.

The CEC will review a safety event dossier, prepared by BSC, which may include copies of subject source documents provided by study sites, core lab results and independent reviewer information as available for the above listed events. The death classification system that will be used by the CEC was developed using the NASPE policy(23), as well as definitions from Epstein et al. (24) and O'Connor et al. (25).

21.3. Data Monitoring Committee

A Data Monitoring Committee (DMC) is responsible for the oversight review of all AEs. The DMC will include leading experts in Electrophysiology and Biostatistics who are not participating in the study and who have no affiliation with BSC. During the course of the study, the DMC will review accumulating safety data to monitor the incidence of AEs sent to the CEC and other trends that would warrant modification or termination of the study. Responsibilities, qualifications, membership, and DMC procedures will be included in the DMC Charter.

Any DMC recommendation for study modification or termination due to concerns over subject safety or issues relating to data monitoring or quality control will be submitted in writing to BSC and the study Principal Investigator for consideration and final decision. If the DMC at any time determines that a potentially serious risk exists to subjects in this study, the DMC chairman will immediately notify both BSC and the Principal Investigator.

21.4. Executive/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 include oversight of the overall conduct of the study with regards 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.

22. Suspension or Termination

22.1. 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.

22.2. Criteria for Premature Termination of the Study

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

- Suspicion of an unacceptable risk, including serious health threat. In this case, the sponsor shall suspend the clinical investigation while the risk is assessed. The sponsor shall terminate the clinical investigation if an unacceptable risk which cannot be controlled is confirmed.
- Instructions by the IRB/EC/REB or regulatory authorities to suspend or terminate the clinical investigation.
- 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 of the device.

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

Any investigator, or associated IRB/EC/REB or regulatory authority 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.

22.4. 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 investigational product to Boston Scientific, unless this action would jeopardize the rights, safety, or welfare of the subjects.

22.5. 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 3 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 study 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.

23. Study Registration and Results Posting

23.1. Study Registration

To comply with applicable laws and regulations, the study will be registered on a publicly accessible database. This research study is registered on http://www.ClinicalTrials.gov, as required by U.S. Law and other jurisdictions.

23.2. Clinical Investigation Report

Study results will be made available in accordance with the legal requirements and the recognized ethical principles, in accordance with the Boston Scientific Policy. A Clinical Investigation Report will be made available to all investigators, IRB/EC/REB and regulatory authorities, as applicable in accordance with the Boston Scientific Policy and local requirements. As applicable an abbreviated Clinical Investigation Report will be made available on a publicly accessible database.

23.3. 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. BSCmay 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/).

24. Reimbursement and Compensation for Subjects

24.1. Subject Reimbursement

Travel and other expenses incurred by subjects as a result of participation in the study may be reimbursed in accordance with pertinent country laws and regulations and per the study site's regulations. Subjects may also be eligible for a subject stipend for their time completing questionnaires and/or assessments as part of the clinical study.

24.2. 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.

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26. Abbreviations and Definitions

26.1. Abbreviations

Abbreviations are shown in **Table 26-1** below.

Table 26-1: Abbreviations and Definitions

Abbreviation/Acronym	Term
AAD	Anti-Arrhythmic Drug
AF	Atrial Fibrillation
AFL	Atrial Flutter
AT	Atrial Tachycardia
CABG	Coronary artery bypass grafting
CRT	Cardiac Resynchronization Therapy
CVA	Cerebral Vascular Accident
DFU	Directions for Use
DMS	Diaphragm Movement Sensor
DVT	Deep Vein Thrombosis
EDC	Electronic Data Capture
EP	Electrophysiology
HRS	Heart Rhythm Society
IB	Investigator's Brochure
ICD	Implantable Cardioverter Defibrillator
ICF	Informed Consent Form
IFU	Instructions for Use
LA	Left Atrium
LVEF	Left Ventricular Ejection Fraction
MRI	Magnetic Resonance Imaging
PAF	Paroxysmal Atrial Fibrillation
PE	Pulmonary Embolism
PTCA	Percutaneous transluminal coronary angioplasty
PV	Pulmonary Veins
PVI	Pulmonary Vein Isolation
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SCE	Silent Cerebral Event
SCL	Silent Cerebral Lesion
TEE	Trans-esophageal echocardiography

Abbreviation/Acronym	Term
TIA	Transient Ischemic Attack

26.2. Definitions

Terms are defined in **Table 26-2** below.

Table 26-2: Abbreviations and Definitions

Term	Definition
Activated Coagulation/Clotting Time	ACT is a test that is used to monitor the effectiveness of high dose heparin therapy.
Acute Procedural Failure	Failure to achieve acute procedural success in the index procedure or repeat procedure during the blanking period
Arterial-Venous Fistula	Abnormal communication between an artery and a vein.
Atrioesophageal Fistula	An atrioesophageal fistula is defined as a connection between the atrium and the lumen of the esophagus. Evidence supporting this diagnosis includes documentation of esophageal erosion combined with evidence of a fistulous connection to the atrium, such as air emboli, an embolic event, or direct observation at the time of surgical repair. A CT scan or MRI scan is the most common method of documentation of an atrioesophageal fistula.
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 any RF application with the study device.
AV block	A conduction disturbance that results in the partial inability of an electrical impulse generated in the atria to reach the ventricles. Refers to AV block not attributable to medication effect or vasovagal reaction.
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.
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 30 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
Index procedure time	Time from first sheath into last catheter removal

Term	Definition
LA dwell time	Time from StablePoint Catheter exiting the sheath in the LA to final PVI
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.
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.
Phrenic Nerve Palsy	Phrenic nerve palsy is defined as absent phrenic nerve function demonstrated radiographically. A phrenic nerve palsy is considered to be permanent when it is documented to be present 12 months or longer following ablation.
Pneumothorax	Collapse of the lung due to an abrupt change in the intrapleural pressure within the chest cavity.
Primary Effectiveness Failure	A TREATMENT subject with • Failure to achieve acute procedural success in the index procedure or repeat procedure during the blanking period • Use of amiodarone post index procedure • Surgical treatment for AF/AFL/AT post index procedure • Use of a non-study ablation catheter for AF targets in the index procedure or repeat procedure during the blanking period • More than one repeat procedure during the blanking period (90 days 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 ECG) between 91 and 183* 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 days post index procedure: • Repeat procedure • Electrical and/or pharmacological cardioversion for AF/AT/AFL • Prescribed any AAD** *If evaluation of primary effectiveness is performed at twelve months then primary effectiveness events will include events seen through 365 days post index procedure. **AADs for endpoint will consist of all Class I/III, including Amiodarone, and any Class II/IV medications taken for control of atrial fibrillation (AF)/Atrial tachycardia (AT)/Atrial flutter (AFL) recurrence.
Prolonged Hospitalization	Hospitalization ≥72 hours after the study procedure for reasons other than anticoagulation

Term	Definition
Pseudoaneurysm	A dilation of an artery with disruption of one or more layers of its walls.
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 edema/heart failure will be considered a primary safety endpoint event when an intervention is required, such as administering diuretics or a prolonged hospitalization.
Severe Pulmonary Vein Stenosis	Severe pulmonary vein stenosis is defined as a reduction of the diameter of a PV or PV branch. PV stenosis can be categorized as mild <50%, moderate 50%–70%, and severe ≥70% reduction in the diameter of the PV or PV branch. A severe PV stenosis will count towards the primary safety endpoint if it is confirmed by imaging.
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.
Stroke/Cerebrovascular accident (CVA)	Stroke diagnostic criteria: • 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) • Stroke: (diagnosis as above, preferably with positive neuroimaging study); o Minor–Modified Rankin score <2 at 30 and 90 days Major–Modified Rankin score ≥2 at 30 and 90 days

Term	Definition
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
Major 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. Appendices

27.1. Indications for ablation of PAF according to 2017 HRS expert consensus statement on catheter and surgical ablation of atrial fibrillation

Indications	Recommendation	class	Level of Evidence
Symptomatic AF refractory or intolerant to at least one Class I or III antiarrhythmic medication	Paroxysmal: Catheter ablation is recommended.	I	A
Symptomatic AF prior to initiation of antiarrhythmic therapy with a Class I or III antiarrhythmic medication	Paroxysmal: Catheter ablation is reasonable	IIa	B-R

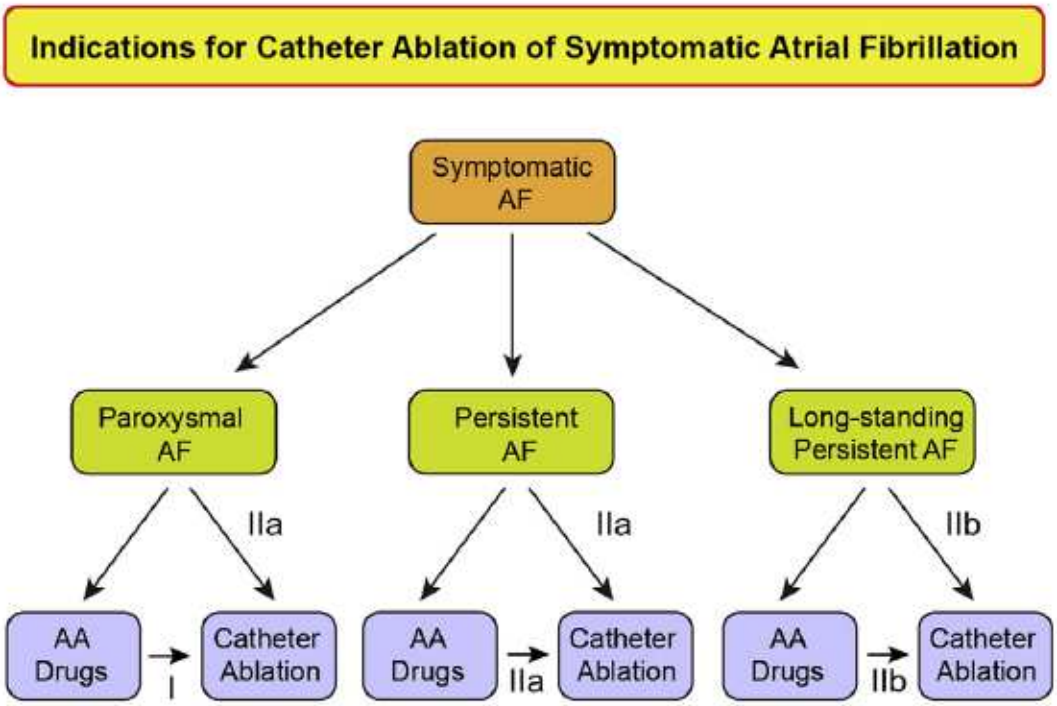

Figure 27-1: Indications for catheter ablation of symptomatic atrial fibrillation

Shown in this figure are the indications for catheter ablation of symptomatic paroxysmal, persistent, and long-standing persistent AF. The Class for each indication based on whether ablation is performed after failure of antiarrhythmic drug therapy or as first-line therapy is shown.

27.2. National Institutes of Health Stroke Assessment

The NIH Stroke Scale (NIHSS) is an assessment tool which quantifies stroke related neurological deficit. This assessment must be conducted in person to provide valuable information on stroke severity.

An Investigator or appropriately trained and delegated designee will administer NIH Stroke Scale assessment prior to the index ablation procedure (Baseline) and again at hospital discharge or Day 1 post Index Procedure, whichever is later. All individuals conducting the assessment will be required to become certified on administration of the assessment and provide BSC with documentation of certification prior to assessment completion with subjects.

Investigational sites will be provided with instructions for assessment completion for the test. They will be instructed to administer stroke scale items in the order listed on the form. Scores should reflect what the subject does, not what the clinician thinks the subject can do. The clinician should record answers while administering the exam and work quickly. Except

where indicated, the subject should not be coached (i.e., repeated requests to subjects to make a special effort). In cases of a worsening NIHHS score, the subject should undergo further assessment to rule out a cerebral event, which may include a neurological consultation and/or assessment through an MRI scan, if deemed appropriate.