POLARx™ Cardiac Cryoablation System Post Market Clinical Study

POLAR SMART

PY007

CLINICAL INVESTIGATION PLAN

NCT#05282823

Sponsored By

Boston Scientific Corporation, Rhythm Management (RM)
4100 Hamline Avenue North
St. Paul, MN 55112
United States

and

Boston Scientific International SA
2, rue René Caudron
Parc d'affaires Le Val Saint-Quentin
78960 Voisins-le-Bretonneux, France

Contact Information

Role	Contact
Clinical Contact	[redacted] Clinical Trial Manager Boston Scientific Asia Pacific Pte Ltd [redacted]
	[redacted]
Coordinating Principal Investigator(s)	**Dr Junichi Nitta** [redacted]
Coordinating Co-Principal Investigator	**Dr Yasuteru Yamauchi** [redacted]
Steering Committee Members	**Dr Masaomi Kimura** [redacted]
	Dr Shinsuke Miyazaki [redacted]
	Professor Young Keun On [redacted]
	Dr Yukihiko Yoshida [redacted]

2. Protocol Synopsis

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Study Objective(s)	To collect real-world clinical data on safety, effectiveness and procedural success of Boston Scientific Cardiac Cryoablation System (POLARx™ System) when used to perform pulmonary vein isolation (PVI) in the ablation treatment of De Novo Atrial Fibrillation (AF).
Indication(s) for Use	Subjects enrolled in this POLAR SMART study will be clinically indicated for PVI ablation procedure (in compliance with instructions for use (IFU)/Tenpubunsyo as legally approved conditions) for the treatment of paroxysmal AF.
(Commercial) Device/System applied as Standard of Care and sizes, if applicable	The Boston Scientific Cardiac Cryoablation System ("Cryoablation System") consists of the following devices and components: • POLARx™ and POLARx™ FIT Cryoablation Catheters ("Cryoablation Catheter"); • POLARMAP™ Catheter ("Cryo Mapping Catheter"); • POLARSHEATH™ Steerable Sheath ("Cryo Steerable Sheath"); • SMARTFREEZE™ Console ("Console"); • Related Accessories, as listed in protocol section 5.1.7.
Study Design	POLAR SMART study is a prospective, multicenter, single arm, post-market study. All subjects signing the consent, undergoing the index (ablation) procedure and treated with the study devices will be followed up for one year.

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	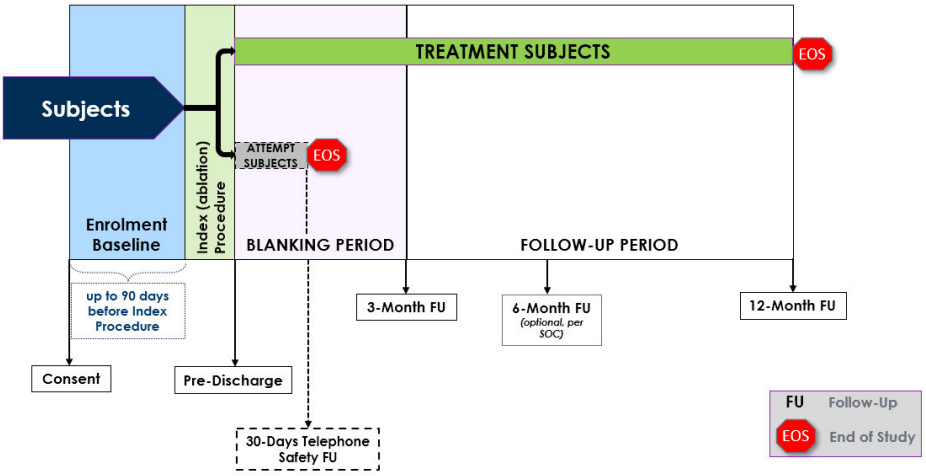 **Figure 7.1-1: POLAR SMART Study Design**
Planned Number of Subjects	A minimum sample size of 200 subjects treated only with PVI is required. The maximum overall study sample size will be limited to ≤ 400 subjects. To avoid any center effect and bias, individual centers will not be allowed to enroll more than 20 subjects meeting enrollment criteria, unless Boston Scientific gives written approval to do so.
Planned Number of Sites / Countries	Approximately 30 sites in Japan and South Korea will be included in the study.
Primary Safety Endpoint	Safety event free rate at 12 months post-index procedure. *Primary safety events will consist of a composite of the following procedure-related and device-related adverse events.* *Acute primary safety endpoint events, events occurring up to 7 days post-index procedure or hospital discharge, whichever is later, include:* • Death • Myocardial infarction (MI) • Gastroparesis/injury to vagus nerve • Transient ischemic attack (TIA) • Stroke/Cerebrovascular accident (CVA) • Thromboembolism/Air embolism* • Cardiac tamponade/perforation • Pneumothorax • Serious vascular access complications**

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	• Pulmonary edema/heart failure • AV block not attributable to medication effect or vasovagal reaction. * Thromboembolic or air embolic events collected in the study refer to any occlusion of blood vessel(s) that results in clinical symptoms. ** Defined as prolongation of hospitalization, requirement of surgical intervention or blood transfusion. *Chronic primary safety endpoint events, events occurring through 12 months post-index procedure, include:* • Atrial esophageal fistula • Significant pulmonary vein (PV) stenosis (≥ 70% reduction of diameter of the PV from baseline*** **OR** presented by patient's symptoms at 12-Month follow-up and requiring intervention) • Symptomatic pericardial effusion • Persistent phrenic nerve injury**** *** Recommended to use the same imaging method as baseline. **** A non-recovered phrenic nerve injury 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.
Primary Effectiveness Endpoint	Failure free rate at 12 months post-index procedure. *Failure defined as:* • Failure to achieve acute procedural success* in the index procedure; • Any documented recurrent AF episode(s), or new onset of atrial flutter (AFL) or any other atrial tachycardia (AT) events (≥ 30 seconds in duration from any clinical recording devices **OR** from a 10-second 12-lead ECG) between Days 91 and 12-Month follow-up**; • Any of the following interventions between Days 91 and 12-Month follow-up: ▪ Repeat AF ablation procedure; ▪ Electrical and/or pharmacological cardioversion of AF or any new AFL, AT; ▪ Prescribed a higher dose of any anti-arrhythmic drugs (AAD)*** documented at baseline or a new AAD*** not documented at baseline.

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	* Acute procedural success is defined as isolation of all the pulmonary veins or anatomical equivalents achieved with the Cryoablation Catheter at the end of the index procedure and as demonstrated at minimum by entrance block using the Cryo Mapping Catheter (Other techniques of assessment are per investigator's discretion). ** Subjects will be monitored for recurrences/new onset of the arrhythmias by means of 12-lead ECG OR any clinical recording devices (for example but not limited to, smart watch, 24-hour Holter monitoring, home monitoring systems or implanted devices etc.) that are per standard of care (SOC) used by the hospital/clinic. These documentation of episodes would need to be verified by investigator and filed in medical records. *** AADs for endpoint will consist of all Class I/III and any Class II/IV medications taken for control of AF/AFL/AT recurrence.
Secondary Endpoints	• Rate of documented acute procedural success, defined as PVI achieved with the Cryoablation System. Electrical isolation of a PV is demonstrated at minimum by entrance block using the Cryo Mapping Catheter (Other techniques of assessment are per investigator's discretion). • Failure free rate at 6 months post-index procedure. ▪ Failure to achieve acute procedural success* in the index ablation procedure; ▪ Any documented recurrence of AF or new onset of any AFL or AT events (≥ 30 seconds in duration from any clinical recording devices or from a 10-second 12-lead ECG) between Days 91 and 6-Month follow-up**; ▪ Any of the following interventions between Days 91 and 6-Month follow-up: o Repeat AF ablation procedure; o Electrical and/or pharmacological cardioversion of AF or any new AFL, AT; o Prescribed a higher dose of any AAD*** documented at baseline or a new AAD*** not documented at baseline. * Acute procedural success is defined as isolation of all the pulmonary veins or anatomical equivalents achieved with the Cryoablation Catheter at the end of the index procedure and as demonstrated at minimum by entrance block using the Cryo Mapping Catheter (Other techniques of assessment are per investigator's discretion). ** Subjects will be monitored for recurrences/new onset of the arrhythmias by means of 12-lead ECG OR any clinical recording devices (for example but not limited to, smart watch, 24-hour Holter monitoring, home monitoring systems or implanted devices etc.) that are per SOC used by the hospital/clinic. These documentation of episodes would need to be verified by investigator and filed in medical records.

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	*** AADs for endpoint will consist of all Class I/III and any Class II/IV medications taken for control of AF/AFL/AT recurrence.
Additional Endpoints	Additional endpoints and analyses include, but are not limited to: • Procedure times: left atrium (LA) dwell time*, total ablation time, number of cryo applications per vein, time to thaw, total fluoroscopy time and total procedure time; • Time-To-Isolation (TTI) per ablation application, if available; • Freedom from recurrence of individual types of AF, or new AFLs or ATs between Days 91 and 12-Month follow-up; • Analysis of additional ablation techniques performed as there is foreseen cavotricuspid isthmus (CTI) and roof line ablation performed with other catheters outside PVI; • Analysis of different anaesthesia techniques (General anaesthesia with or without intubation versus sedation); • Freedom from AF recurrence in subjects with anatomical variants of PV such as, but not limited to, common ostia, additional pulmonary vein or early branching; • Freedom from primary effectiveness failure evaluated in subgroups of subjects (termination of AAD versus continuation of AAD after blanking period); • For subjects undergoing 3D mapping with the Boston Scientific Rhythmia Mapping System and performing a post-procedural map, map information will be collected to determine lesion locations; • The percentage of subjects that undergo repeat ablation during the course of the clinical follow-up; • More than one repeat procedure during the blanking period (within 90 days post-index procedure); • Changes in the quality of life measures (AFEQT and EQ-5D-5L) between baseline and 12-Month follow-up; • The percentage of subjects experiencing device-related adverse events; • Comparison of procedural and therapy success between POLAR ICE (NCT04250714) and POLAR SMART.

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	* LA dwell time is defined as time from the Cryoablation Catheter introduced in the left atrium (LA) to the last time of Cryoablation Catheter exiting the LA.
Method of Assigning Subjects to Treatment	All subjects who meet the eligibility criteria and sign the consent form, has the study device inserted into the body and undergoes protocol specific treatment (cryoablation) for the intended disease will be assigned to the TREATMENT group.
Follow-up Schedule	Visits schedule: • Enrollment and Baseline clinic visit, baseline visit can be on the same day as enrollment visit, however the Informed Consent must be signed and dated prior to conducting any study related activities (up to 90 days before Index Procedure); • Index (Ablation) procedure (day 0); • Pre-discharge visit must be done before hospital discharge (required); • 3 months follow-up visit (recommended in-clinic follow-up visit if done as per SOC, at a minimum a telephone contact follow-up is required); • 6 months follow-up visit (optional, this can be either a in-clinic follow-up visit or a telephone contact follow-up as per SOC); • 12 months in-clinic follow-up visit (required); • An additional follow-up visit (any subject visit triggered by subject symptoms, clinical events or per SOC that is not already defined as one of the study visits at the investigational site).
Study Duration	Enrollment is expected to be completed in approximately 12 months and total study duration with all follow-up data collected is estimated to be approximately 36 months.
Participant Duration	The study duration for each subject is expected to be approximately 12 months.
Inclusion Criteria	1. Subjects indicated for the treatment of AF with the cryoablation system; 2. Subjects who are willing and capable of providing informed consent;

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	3. Subjects who are willing and capable of participating in all testing associated with this clinical study at an approved clinical investigational center; 4. Subjects who are of legal age to give informed consent specific to the national law.
Exclusion Criteria	1. Any known contraindication to an AF ablation or anticoagulation, including those listed in the IFU/Tenpubunsyo as legally approved conditions; 2. Any prior LA ablation; 3. AF secondary to electrolyte imbalance, thyroid disease, or any other reversible or non-cardiac cause; 4. Known or pre-existing severe PV Stenosis; 5. Evidence of cardiac myxoma, LA thrombus or intracardiac mural thrombus; 6. Previous cardiac surgery (e.g. ventriculotomy or atriotomy, CABG, PTCA, PCI, ventricular fistula or atrial incision) and any surgery within 90 days prior to enrollment; 7. Any implanted cardiac device (e.g. PM, ICD, CRT, valve replacement, LAAO, etc) within 90 days prior to enrollment; 8. Any planned OR scheduled cardiac device procedure (e.g. PM, ICD, CRT, valve replacement, LAAO, etc) during and post PVI ablation (during and post-index procedure); 9. Any planned ablation in LA except PVI procedure and roof line ablation; 10. Any planned ablation in ventricles; 11. Subjects undergoing atrial septal defect patch or other surgical procedures at or near the atrial septal defect; 12. Subjects with severe valvular disease OR with a prosthetic – mechanical or biological - heart valve (not including valve repair and annular rings); 13. Presence of any pulmonary vein stents; 14. Subjects with active systemic infection; 15. Subjects that have vena cava embolic protection filter devices and/or known femoral thrombus;

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	16. Any previous history of cryoglobulinemia; 17. Subjects that are unable to undergo atrium access safely or operate in the atrium as per investigator's medical judgement; 18. Subjects with no vascular access or obstruction of the femoral vein; 19. Subjects with blood coagulation disorders or diseases; 20. Any prior history of documented cerebral infarct, TIA or systemic embolism (excluding a post-operative deep vein thrombosis (DVT)) ≤ 180 days prior to enrollment; 21. Subjects who are hemodynamically unstable; 22. Subject is unable or not willing to complete follow-up visits and examination for the duration of the study; 23. Subjects with life expectancy ≤ 1 year per investigator's medical judgement; 24. Women of childbearing potential who are, or plan to become, pregnant during the time of the study (assessment per investigator's discretion); 25. Subjects with unrecovered/unresolved Adverse Events (AE) from any previous invasive procedure; 26. Subjects who are currently enrolled in another investigational study or registry that would directly interfere with POLAR SMART study. Exception 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 for approval.
Statistical Methods	
Primary Statistical Hypothesis	There are no formal hypotheses.
Statistical Analysis Methods	Time-to-event endpoints will be summarized using Kaplan-Meier event-free rates with 2-sided 95% pointwise log-log confidence limits. Summary statistics will be presented for secondary and additional endpoints. E.g. event rates and confidence intervals will be provided for

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	binary endpoints, and mean ± SD and/or min, max, and median and quartiles will be presented for continuous endpoints.
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4. Introduction

4.1. *Background*

Evidences suggest AF is among the most prevalent arrhythmias in the world today. European Society of Cardiology (ESC) Guidelines 2020 has summarized (2): "The estimated prevalence of AF in adults currently ranges between 2% and 4% (globally, 46.3 million individuals had prevalent AF and AFL in 2016)" (3). A 2.3-fold rise (4) is expected in the coming decades (5,6) largely owing to extended longevity of the general population and intensifying search for undiagnosed AF (7). The age of patients with AF is steadily rising and now averages between 75 and 85 years of age (8). AF symptoms arise from the rapid, irregular rhythm as well as cardiac hemodynamic changes related to uncoordinated atrial contractions. These uncoordinated contractions also allow blood to pool in the atria and may ultimately lead to thromboembolism and stroke. AF impairs quality of life (9), associates with a five-fold risk of stroke, a three-fold incidence of congestive heart failure, and higher mortality. AF is a progressive disease, with almost all cases starting as paroxysmal, which then progresses to persistent and long-standing persistent types (10).

In Asia, the estimates prevalence of AF have suggested that, by 2050, 72 million individuals (11) in Asia will be diagnosed with AF, more than double the combined numbers of patients in Europe and the United States. This estimate increase is attributed to the proportionally larger aged population in Asian countries. With this, the prevalence of AF is expected to increase in Japan and South Korea as the population ages.

Recent results are showing that catheter ablation was effective in recurrence of any AF compared to drug treatment over 5 years of follow up (12). Among patients with AF, the strategy of catheter ablation, compared with medical therapy, significantly reduce death, disabling stroke, serious bleeding, or cardiac arrest if catheter ablation was successfully done in a per protocol analysis (13).

Most recent guidelines from the ESC and Japan Circulation Society (JCS)/Japan Heart Rhythm Society (JHRS) for the management of AF state that catheter ablation of AF is effective in restoring and maintaining sinus rhythm in patients with symptomatic paroxysmal, persistent, and probably long-standing persistent AF, in general as second-line treatment after failure of or intolerance to antiarrhythmic drug therapy (14). In particular, it has been increasingly recognized that focal PV 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 (1), electrical isolation of the pulmonary veins is now recognized as the cornerstone of AF ablation.

Large randomized controlled trials have confirmed the superiority of catheter ablation in (9) maintaining sinus rhythm, as well as improving symptoms, exercise capacity, and quality of life (15) in comparison to AADs. In ESC, HRS and JCS/JHRS guidelines(1,2,14,16), catheter ablation is strongly recommended for patients with symptomatic AF after an adequate trial of AAD therapy.

With the understanding that PVIs may be the "cornerstone" of ablation strategies, a cryo balloon has been developed to provide a "single shot" therapy for isolation of the PVs. By navigating the balloon to the ostium of the PV and occluding flow, a PV may be isolated with a single cryoablation of 3 to 4 minutes. The currently approved technology (Artic Front™/ Arctic Front Advance™ Cryoablation Balloon, Medtronic®) has completed two landmark studies demonstrating efficacy for paroxysmal AF management of approximately 70% and 65% respectively (17,18). In addition to this, the currently approved technology (Artic Front™/ Arctic Front Advance™ Cryoablation Balloon, Medtronic®) has also completed a postmarketing surveillance study in Japan showing that the success rate in the acute phase of PVI was > 99%, and that the sinus rhythm maintenance effect in the 6-month follow-up including the 3-month blanking period was good at approximately 88% (19).

Boston Scientific Cardiac Cryoablation System, POLARx™ is available in Europe market since 2020 and Japan market since October 2021. The novel POLARx™ showed similar safety and efficacy compared to the Arctic Front Cryoballoon. A higher rate of real-time PV recordings and significantly lower minimal balloon temperatures were observed using the POLARx™ (20,21,22,23).

Complications arising from cryoablation are consistent with those of heat-based therapies. Additionally, as the balloon is placed in the right-sided PVs and near the phrenic nerve, diaphragm paralysis, (both transient and permanent), has been reported. To mitigate this risk, pacing maneuvers and continuous analysis of diaphragmatic movement has been used.

Catheter and sheath performance for cryoablation balloon procedures has not changed since the begining, more than ten years ago. Knowing that electrophysiologists are familiar with treating AF with cryo-therapy, the Boston Scientific Cardiac Cryoablation System was designed with a clinical user focus and set out to improve the user experience. This was accomplished by improving balloon stability and achieving continuous inflation and uniform balloon pressure during all phases of the cryoablation, improving sheath maneuverability and incorporating general safety/ workflow improvements over current technology.

Extensive pre-clinical and performance bench testing studies have been performed to date. A first-in-man clinical study was completed on 30 patients with one month follow-up in 2018 and its data has been used to obtain CE-mark. Ongoing trials on safety and effectiveness are POLAR ICE, NCT04250714 (completed enrollment of 400 subjects in May 2021) and FROZEN-AF, NCT04133168 (completed enrollment of 325 subjects in August 2021). Both trials are multicenter, single arm cohort trials with defined measures and follow up schedules and subjects are recruited in multiple geographies. POLAR ICE will provide post market data for support of continued safety and effectiveness assessment for the Boston Scientific Cryoablation System, when used in a clinical trial follow up in SOC indicated patients in Europe. POLAR SMART study will provide real-world clinical data on safety, effectiveness and procedural success of Boston Scientific Cardiac Cryoablation System when used under SOC in Japan and South Korea to support clinical equivalence of results under different clinical care and ethnic conditions.

4.2. *Study Rationale*

The goal of any novel design or therapeutic strategy for AF is to restore normal sinus rhythm and to reduce or eliminate the symptoms due to rapid atrial response.

Boston Scientific developed a Cryoablation Balloon that can maintain stability and achieve continuous inflation and uniform pressure during the entire procedure. A cryoablation balloon that has been designed to maintain uniform pressure is likely to provide improved stability during all phases of the cryoablation, improving user experience and preserving the proven design validated by the Medtronic® Arctic Front Advance™ Catheter.

Majority of the above BSC POLARx™ system studies data were collected predominantly in North American and European populations, it will be necessary to collect systematic scientific evidence unique to Japan and South Korea to proactively capture the impact on medical outcomes driven by socio-economic, healthcare and epidemiological differences. This evidence will be shared with the local electrophysiologist to enable better outcomes. Additionally POLAR SMART data can also support post-market clinical follow-up (PMCF) data collection.

The POLAR SMART post market study intends to collect real-world clinical data on safety, effectiveness and procedural success of Boston Scientific Cardiac Cryoablation System (POLARx™ System) when used to perform PVI in the ablation treatment of De Novo AF.

5. Device Description

5.1. *Commercial Device Under Study*

The Boston Scientific Cardiac Cryoablation System (henceforth “Cryoablation System”) is indicated for cryoablation and electrical mapping of the pulmonary veins for PVI in the ablation treatment of AF as per current and future guidelines and system IFU/ Tenpubunsyo.

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

The article/model names (components) and accessories of the Cryoablation system and their associated model numbers are listed in Table 5.1-1. For any upcoming available commercial new article/model names and their associated model numbers, only administrative changes are required to the table below and these do not qualify to amend the protocol and send for any EC/IRB approval.

Please refer to IFU/Tenbubunpsyo for locally approved system overview.

Table 5.1-1: Cryoablation System Components and Accessories

Article/ Model names (Component)	BSC Model Number
POLARx™ Cryoablation Catheter (Cryoablation Catheter)	M004CRBS2000 (Short tip) M004CRBS2100 (Long tip)
POLARx™ FIT Cryoablation Catheter (Cryoablation Catheter)	M004CRBS2010 (Short tip) M004CRBS2110 (Long tip)
SMARTFREEZE™ Cryo Console (Console)	M004CRBS4000
POLARMAP™ Mapping Catheter (Cryo Mapping Catheter)	M004CRBS7200
POLARSHEATH™ Steerable Sheath (Cryo Steerable Sheath)	M004CRBS3050
Accessories	**BSC Model Number**
Diaphragm Movement Sensor (DMS)	M004CRBS6110
Inter Connection Box (ICB)	M004CRBS4110
Remote Control for Inter Connection Box	M004CRBS4120
Inter Connection Box (ICB) 5 port	M004CRBS4130
SMARTFREEZE Cryo-Console Foot Switch	M004CRBS4200
Cryo-Cable	M004CRBS5200
Cryo-Catheter Extension Cable	M004CRBS5100
POLARMAP™ EP Electrical Cable	M004CRBS6200
Esophageal Temperature Sensor (ETS)	M004CRBS6310
Esophageal Temperature Sensor (ETS) extension Cable	M004CRBS6320
Esophagus Temperature Sensor Cable for CIRCA-S	M004CRBS6340
Software for the SMARTFREEZE™ Cryo Console	The Software is part of the SMARTFREEZE Cryo Console (M004CRBS4000) and is not listed separately.

5.1.1. POLARx™ and POLARx™ FIT Cryoablation Catheters (Cryoablation Catheter)

The Cryoablation Catheter is a component of the Boston Scientific Cardiac Cryoablation System ("Cryoablation System") and is a single use, flexible, over-the-wire balloon catheter used to ablate cardiac tissue. The Cryoablation Catheter is used in conjunction with the Console

to induce thermal injury and endocardial tissue necrosis when the balloon is in contact with cardiac tissue and reaches cryoablation temperatures created by a refrigerant injected from the Console into the balloon segment of the POLARx™. The Cryoablation catheter connects to the Console with a Cryo-Cable (for N_2O delivery and removal) and an Extension Cable (for electrical connection via the Interconnection Box). The Cryoablation catheter is designed to be used as a circular mapping catheter deployed within the guidewire lumen during ablation procedures.

The POLARx™ FIT Cryoablation Catheters are additional models (Short Tip and Long Tip) of the POLARx™ cryoablation balloon catheters that are part of the POLARx™ cryoablation system. The POLARx™ FIT catheter is identical to the predicate POLARx™ catheter with the exception that it can be inflated to a larger balloon diameter of 31 mm.

During an electrophysiology (EP) ablation procedure, the Cryoablation Catheter (including the Cryo Mapping Catheter) is inserted through the Cryo Steerable Sheath (POLARSHEATH™) into the venous system, directed into the LA and towards the ostium of the target PV. Once positioning that occludes the PV has been verified, refrigerant is delivered through the Cryo-Cable to the injection coil, which directs the flow of refrigerant toward the interior distal surface of the balloon. This results in a cooled region at the balloon tissue interface, which adheres to the endocardial surface. The low temperature and pressure gradient allows the balloon to thermally create transmural, circumferential tissue necrosis (lesions) and interrupt electrical conduction.

The Cryoablation Catheter is comprised of the following major components, distal to proximal:

- Atraumatic tip
- Double layer balloon system
- Guide wire lumen
- Internal balloon thermocouple
- Injection coil and manifold for delivery of the refrigerant; liquid nitrous oxide (N_2O)
- Catheter shaft; to retrieve the expanded N_2O gas
- Catheter handle
- Distal handle connections

Figure 1: Cryoablation Catheter Distal Tip

Figure 2: Cryoablation Catheter Handle

Table 5.1-2: POLARx™ Cryoablation Catheter Specifications

Balloon diameter	28 mm
Nominal Distal Tip Length M004CRBS2000 (Short tip)	5 mm
M004CRBS2100 (Long tip)	12 mm
Shaft diameter	0.164 in /12.5 F
Working length	99 cm

Table 5.1-2: POLARx™ FIT Cryoablation Catheter Specifications

Inflated Balloon diameter	28/31 mm
Nominal Distal Tip Length M004CRBS2010 (Short tip)	5 mm
M004CRBS2110 (Long tip)	12 mm
Shaft diameter	0.167 in /12.7 F
Working length	99 cm

5.1.2. POLARMAP™ Mapping Catheter (Cryo Mapping Catheter)

The Cryo Mapping Catheter is a single-use, sterile, multi-electrode, diagnostic catheter designed to map cardiac signals during ablation procedures. The catheter is provided in a 20 mm diameter with 8 evenly spaced radiopaque electrodes. The proximal end of the handle contains an electrical connection that integrates with EP lab recording systems. Once deployed through the central guidewire lumen of the Cryoablation Catheter and into the PV, a circular shape is established such that the electrodes contact the endocardial surface. This allows for

recording and interrogation of electrical conduction between the LA and the pulmonary veins. The Cryo Mapping Catheter also allows for delivery of pacing stimuli used in the interpretation of PVI.

Figure 3: Mapping Catheter Assembly

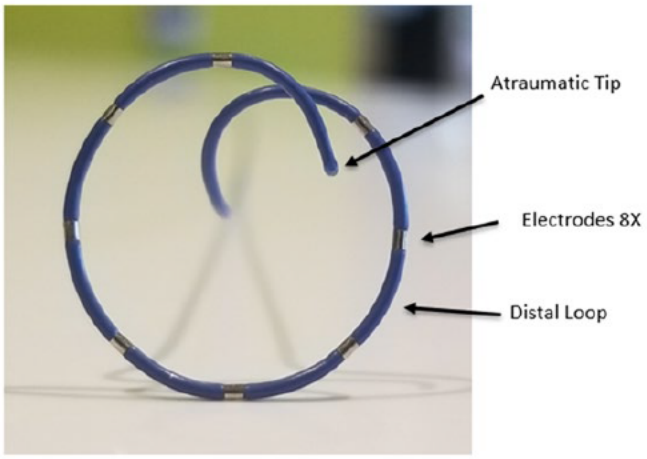

Figure 4: Cryo Mapping Catheter with Electrode Arrangements

Table 5.1-3: Cryo Mapping Catheter Specifications

Catheter Model Number	Catheter Diameter	Evenly Spaced Electrodes
M004CRBS7200	20 mm	8

5.1.3. POLARSHEATH™ Steerable Sheath (Cryo Steerable Sheath)

The Cryo Steerable Sheath is a single use, disposable, steerable percutaneous introducer sheath designed for additional maneuverability of standard catheters that are advanced through the sheath and into cardiac chambers. It is comprised of a composite structured single lumen shaft, an ergonomic handle to provide torque and active deflection, and a hemostasis valve to allow safe introduction, withdrawal, and swapping of catheters and wires while preventing air ingress and minimizing blood loss. A side-port is integrated to allow continuous drip infusion, injection through the center lumen, flushing, aspiration, blood sampling and pressure monitoring.

As a component of the Cryoablation System, the Cryo Steerable Sheath is intended to facilitate the placement of diagnostic and/or therapeutic intracardiac devices during percutaneous catheter ablation procedures. The device is indicated for left-sided cardiac procedures via a transseptal approach.

Table 5.1-4: Cryo Steerable Sheath Specifications

Inner diameter	0.165 in / 13.2 F
Outer diameter	0.208 in / 16.0 F
Working length	68 cm
Total length	82 cm
Dilator working length	85 cm
Reach at 90°	4.6 cm
Guidewire compatibility	0.035 in

5.1.4. SMARTFREEZE™ Cryo Console (Console)

The Console is a device that uses N_2O provided from a refillable cylinder to safely pressurize (inflate) and cool the Cryoablation Catheter to cryogenic ablative temperatures. The Console houses the electrical components and software/firmware needed to perform cryoablation procedures. It controls the delivery, recovery, and disposal of N_2O (cryoablation refrigerant) safely and efficiently. The Console user interface provides a means for initiating and ceasing refrigerant delivery. Once the command is received from the console, N_2O is delivered as a chilled liquid to the Cryoablation Catheter for a programmable time duration. The user interface also displays key information allowing the operator to focus attention on critical tasks and speed up the overall procedure.

Figure 5: Cryo Console

Integration between the Cryoablation Catheter and the Console includes monitoring catheter as well as console functionality, aided by a number of components such as: power cords, extension cables, inter connection box, foot switch, diaphragm movement sensor, esophageal temperature monitor, scavenging hose, wrench and nitrous oxide tanks.

5.1.5. Diaphragm Movement Sensor

The DMS is a patch device placed on the patient just below the costal cartilage on the right side and used to monitor a phrenic nerve pacing response. It is connected to the ICB sending data to be displayed on the user interface of the Console. By integrating the information into the Cryo Console, the user can be informed when the measured pacing response is lower than a pre-determined value set by the physician.

Phrenic nerve monitoring is a known and essential component in determining safety during a cryoablation procedure. The current SOC technique which is used to monitor for phrenic nerve palsy is to have the physician place his/her hand on the subject's abdomen and assess the subject's diaphragmatic movement during the period within the procedure that requires the physician's full attention (when ablation is occurring).

It has been reported with cryoablation balloon technology that the incidence of permanent phrenic nerve injury occurs in up to 0.4% of the cases (10) of patients undergoing a cryoablation procedure. The physician subjectively decides when injury may be occurring

based on the change in diaphragmatic movement during respiration. The physician suspends ablation if there is a significant reduction in diaphragmatic movement. This is a manual and physician dependent technique where the incidence of occurrence is related to experience in the cryoablation procedure.

An accelerometer in the DMS detects any reduction of diaphragmatic movement indicating phrenic nerve impact, thus helping to reduce procedure related adverse events and potentially improve procedural safety. The DMS is connected to the ICB of the Cryo-Console and sends data to be displayed on the Cryo-Console's user interface (see Figure 6 below).

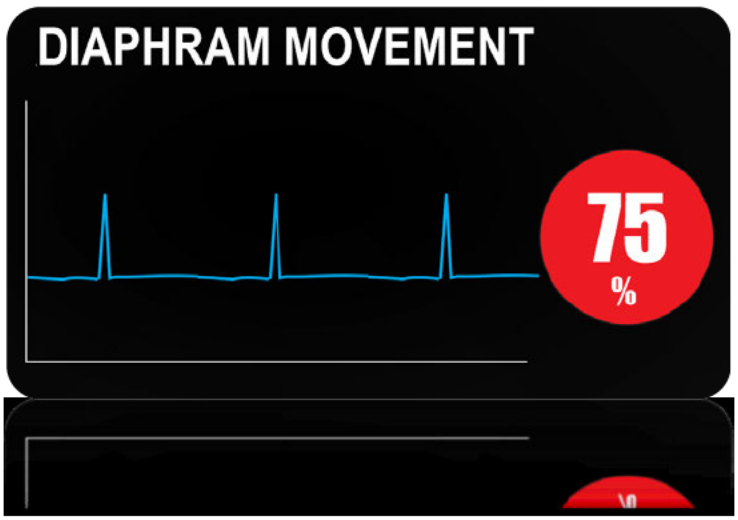

Figure 6: Diaphragm Movement Sensor (DMS) Display

By integrating the information into the Console, the physician can be informed when the measured pacing response falls below a pre-set value. The pre-determined value is programmed by the physician. The value is displayed as a percentage; with the first physical excursion establishing the baseline at 100%. The measurement display changes from "Blue" to "Red" if the value falls below the physician's programmed pre-set value (see Figure 6 above).

The DMS is designed to be used as an adjunct accessory to continually evaluate diaphragm movement during ablation; as a reminder alert to augment the established clinical practice described above for phrenic nerve assessment. The DMS is not a substitute for physician SOC practice of phrenic nerve assessment during a cryoablation; i.e. physician palpation of the diaphragm, or attentive medical practice.

5.1.6. Esophageal Temperature Monitoring Sensor (ETS)

Esophageal temperature monitoring is a frequently used technique, especially when there is an anatomical concern related to the proximity of the esophagus to the inferior PVs and posterior wall of the LA. The esophageal ulceration is generally reversible, with a reported incidence of 17% of patients (10).

This feature integrates the detection of the esophageal temperature and provides a reminder alert to the physician if the esophageal temperature goes below a physician pre-set value. The measured esophageal temperature turns the measurement display from "Blue" to "Red" if the temperature probe falls below a physician pre-set value. This feature potentially reduces adverse events such as esophageal ulcerations and fistulas. This is a optional safety alert system to the measurement systems used today although the alert is now displayed on the Console.

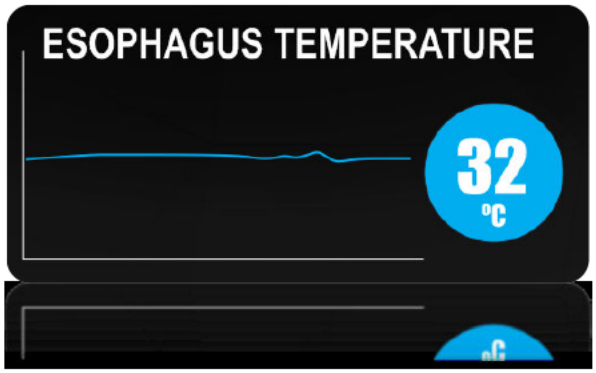

Figure 7: Esophagus Temperature Sensor (ETS) Display

As noted below, the ICB is designed to receive information from other proprietary devices such as an esophageal temperature probe. When connected, the esophageal temperature probe provides monitoring and alert data to the console for display. Esophageal temperature probes are widely available in stand-alone measurement systems and used as such within the EP lab.

The Esophageal Temperature Sensor Cable enables the connection of a commercially available 400 series temperature probe to be connected to the Console.

5.1.7. Other Cryoablation System Components

5.1.7.1. Inter Connection Box (ICB)

The ICB interfaces the Cryoablation Catheter with the Console. It receives the Catheter monitoring signals, DMS data, as well as information from other proprietary devices such as an esophageal temperature probe, a tip pressure sensor and various other safety systems. The ICB then transmits this information to the Console for display and user analysis.

5.1.7.2. Console Foot Switch

The Console Foot Switch interfaces with the Console and allows the user to inflate the Cryoablation Catheter, start and stop flow of N_2O (cryoablation) as well as deflate the Cryoablation Catheter at the conclusion of the ablation.

5.1.7.3. Console Scavenging Hose

The Console Scavenging Hose is a flexible N_2O exhaust line that connects to the hospital gas scavenging system and allows removal of N_2O gas.

5.1.7.4. Cryo Cable

The Cryo Cable is a sterile, single-use cable that provides the connectivity between the Cryoablation Catheter to the Console to support the delivery of liquid refrigerant and the evacuation of remaining N_2O gas.

5.1.7.5. Cryoablation Catheter Electrical Cable

The Cryoablation Catheter Electrical Cable is a sterile, single-use cable that provides the connectivity between the Cryoablation Catheter and the Console ICB.

5.1.7.6. Cryo Mapping Catheter EP Electrical Cables

The EP Electrical Cable is a sterile, single-use accessory for the Cryo Mapping Catheter and is designed to interface (connect) the Cryo Mapping Catheter with EP recording systems.

6. Study Objectives and Endpoints

6.1. *Study Objective*

The study objective is to collect real-world clinical data on safety, effectiveness and procedural success of Boston Scientific Cardiac Cryoablation System (POLARx^{TM} System) when used to perform PVI in the ablation treatment of De Novo AF.

6.2. *Study Endpoints*

6.2.1. Primary Safety Endpoint

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

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

Acute primary safety endpoint events, events occurring up to 7 days post-index procedure or hospital discharge, whichever is later, include:

- Death
- Myocardial infarction (MI)
- Gastroparesis / injury to vagus nerve
- Transient ischemic attack (TIA)
- Stroke / Cerebrovascular accident (CVA)
- Thromboembolism / Air embolism*
- Cardiac tamponade / perforation
- Pneumothorax
- Serious vascular access complications**
- Pulmonary edema / heart failure
- AV block not attributable to medication effect or vasovagal reaction

* Thromboembolic or air embolic events collected in the study refer to any occlusion of blood vessel(s) that results in clinical symptoms.

** Defined as prolongation of hospitalization, requirement of surgical intervention or blood transfusion.

Chronic primary safety endpoint events, events occurring through 12 months post-index procedure, include:

- Atrial esophageal fistula
- Significant PV stenosis (≥ 70% reduction of diameter of the PV from baseline*** **OR** presented by patient's symptoms at 12-Month follow-up and requiring intervention)
- Symptomatic pericardial effusion
- Persistent phrenic nerve injury****

*** Recommended to use the same imaging method as baseline.

**** A non-recovered phrenic nerve injury 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.

6.2.2. Primary Effectiveness Endpoint

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

Failure defined as:

- Failure to achieve acute procedural success* in the index procedure;
- Any documented recurrent AF episode(s), or new onset of AFL or AT events (≥ 30 seconds in duration from any clinical recording devices **OR** from a 10-second 12-lead ECG) between Days 91 and 12-Month follow-up;
- Any of the following interventions between Days 91 and 12-Month follow-up:
  - Repeat AF ablation procedure;
  - Electrical and/or pharmacological cardioversion for AF or new AFL, AT;
  - Prescribed a higher dose of any AAD*** documented at baseline or a new AAD*** not documented at baseline.

* Acute procedural success is defined as isolation of all the pulmonary veins or anatomical equivalents achieved with the Cryoablation Catheter at the end of the index procedure and as demonstrated at minimum by entrance block using the Cryo Mapping Catheter (Other techniques of assessment are per investigator's discretion).

** Subjects will be monitored for recurrences/new onset of the arrhythmias by means of 12-lead ECG OR any clinical recording devices (for example but not limited to, smart watch, 24-hour Holter monitoring, home monitoring systems or implanted devices etc.) that are per standard of care (SOC) used by the hospital/clinic. These documentation of episodes would need to be verified by investigator and filed in medical records.

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

6.2.3. Secondary Endpoints

- Rate of documented acute procedural success, defined as pulmonary vein isolation achieved with the Cryoablation System. Electrical isolation of a PV is demonstrated at minimum by entrance block using the Cryo Mapping Catheter (Other techniques of assessment are per investigator's discretion).
- Failure free rate collected at 6 months post-index procedure.
  - Failure to achieve acute procedural success* in the index procedure;
  - Any documented recurrent AF episode(s), or new onset of AFL or AT events (≥ 30 seconds in duration from any clinical recording devices **OR** from a 10-second 12-lead ECG) between Days 91 and 6-Month follow-up**;
  - Any of the following interventions between Days 91 and 6-Month follow-up:
    - Repeat AF ablation procedure;
    - Electrical and/or pharmacological cardioversion for AF or new AFL, AT;
    - Prescribed a higher dose of any AAD*** documented at baseline or a new AAD*** not documented at baseline.

* Acute procedural success is defined as isolation of all the pulmonary veins or anatomical equivalents achieved with the Cryoablation Catheter at the end of the index procedure and as demonstrated at minimum by entrance block using the Cryo Mapping Catheter (Other techniques of assessment are per investigator's discretion).

** Subjects will be monitored for recurrences/new onset of the arrhythmias by means of 12-lead ECG OR any clinical recording devices (for example but not limited to, smart watch, 24-hour Holter monitoring, home monitoring systems or implanted devices etc.) that are per standard of care (SOC) used by the hospital/clinic. These documentation of episodes would need to be verified by investigator and filed in medical records.

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

6.2.4. Additional Endpoints

Additional endpoints and analyses include, but are not limited to:

- Procedure times: LA dwell time*, total ablation time, number of cryo applications per vein, time to thaw, total fluoroscopy time and total procedure time;
- TTI per ablation application, if available;
- Freedom from recurrence of individual types of AF, or new AFLs or ATs between Days 91 and 12-Month follow-up;
- Analysis of additional ablation techniques performed as there is foreseen CTI and roof line ablation performed with other catheters outside PVI;
- Analysis of different anaesthesia techniques (General anaesthesia with or without intubation versus sedation);
- Freedom from AF recurrence in subjects with anatomical variants of PV such as, but not limited to, common ostia, additional pulmonary vein or early branching;
- Freedom from primary effectiveness failure evaluated in subgroups of subjects (termination of AAD versus continuation of AAD after blanking period);
- For subjects undergoing 3D mapping with the Boston Scientific Rhythmia Mapping System and performing a post-procedural map, map information will be collected to determine lesion locations;
- The percentage of subjects that undergo repeat ablation during the course of the clinical follow-up;
- More than one repeat procedure during the blanking period (within 90 days post-index procedure);
- Changes in the quality of life measures (AFEQT and EQ-5D-5L) between baseline and 12 months follow up;
- The percentage of subjects experiencing device-related adverse events;
- Comparison of procedural and therapy success between POLAR ICE (NCT04250714) and POLAR SMART.

* LA dwell time is defined as time from the Cryoablation Catheter introduced in the LA to the last time of Cryoablation Catheter exiting the LA.

Table 6.2-1 Overview of objectives and endpoints

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To establish continued safety of the cryoablation System in Asian geographies	Event free rate of a composite of procedure and device study specific adverse events (acute: 7 days and chronic: 12 months follow-up)	Majority of the BSC POLARx™ system studies data were collected predominantly in North American and European populations, it will be necessary to collect systematic scientific evidence unique to Japan and South Korea to proactively capture the impact on medical outcome driven by socio-economic, healthcare and epidemiological differences
To collect continued effectiveness data of the Cryoablation System	Failure-free rate at 12 months including: i. failure to achieve success at index procedure, ii. documented AF/AFL/AT iii. interventions to treat these arrhythmias after blanking period, including repeated procedures cardioversion or prescription of new anti-arrhythmic drugs (or higher dose)	
Secondary		
Acute procedural success	Success of procedure (PVI)	Component of the primary effectiveness endpoint
To collect continued effectiveness data of the Cryoablation System	Failure-free rate at 6 months including failure to achieve success at index procedure, documented AF/AFL/AT or interventions to treat these arrhythmias after blanking period, including repeated procedures cardioversion or prescription of new anti-rrhythmic drugs (or higher dose)	To determine potential early benefits comparing to 12 months that has been established by the HRS consensus document.
Additional		
Quality of life assessment	Changes in the quality of life measures (AFEQT and EQ-5D-5L) between baseline and 12 months follow up	Relief from symptoms is one of the main ouotcomes reported of AF ablation

7. Study Design

The POLAR SMART study is a prospective, multicenter, single arm, post-market study.

All subjects signing the consent, undergoing the index (ablation) procedure and treated with the study devices will be followed up for one year.

7.1. *Scale and Duration*

- A minimum sample size of 200 subjects treated only with PVI is required. The maximum overall study sample size will be limited to ≤ 400 subjects.
- To avoid any center effect and bias, individual centers will not be allowed to enroll more than 20 subjects meeting enrollment criteria, unless Boston Scientific gives written approval to do so. The enrollment period is approximately 12 months.
- Approximately 30 sites in Japan and South Korea.
- Total expectation duration of study with all follow-up data collected is estimated to be approximately 36 months.
- The study duration for each subject is expected to be approximately 12 months. Each subject will be followed up at:
    - Enrollment and Baseline clinic visit, baseline visit can be the same day as enrollment visit, however the Informed Consent must be signed and dated prior to conducting any study related activities (up to 90 days before Index Procedure);
    - Index (Ablation) procedure (day 0);
    - Pre-discharge visit must be done before hospital discharge (required);
    - 3 months follow-up visit (recommended in-clinic follow up visit if done as per SOC, at a minimum a telephone contact follow-up is required.) This telephone contact follow-up would only be required if in-clinic follow-up was not done;
    - 6 months follow-up visit (optional, this can be either a in-clinic follow-up visit or a telephone contact follow-up as per SOC)
    - 12 months in-clinic follow-up visit (required);
    - An additional follow-up visit at the investigational site is any subject visit triggered by subject symptoms, clinically events or per SOC that is not already defined as one of the study visits.

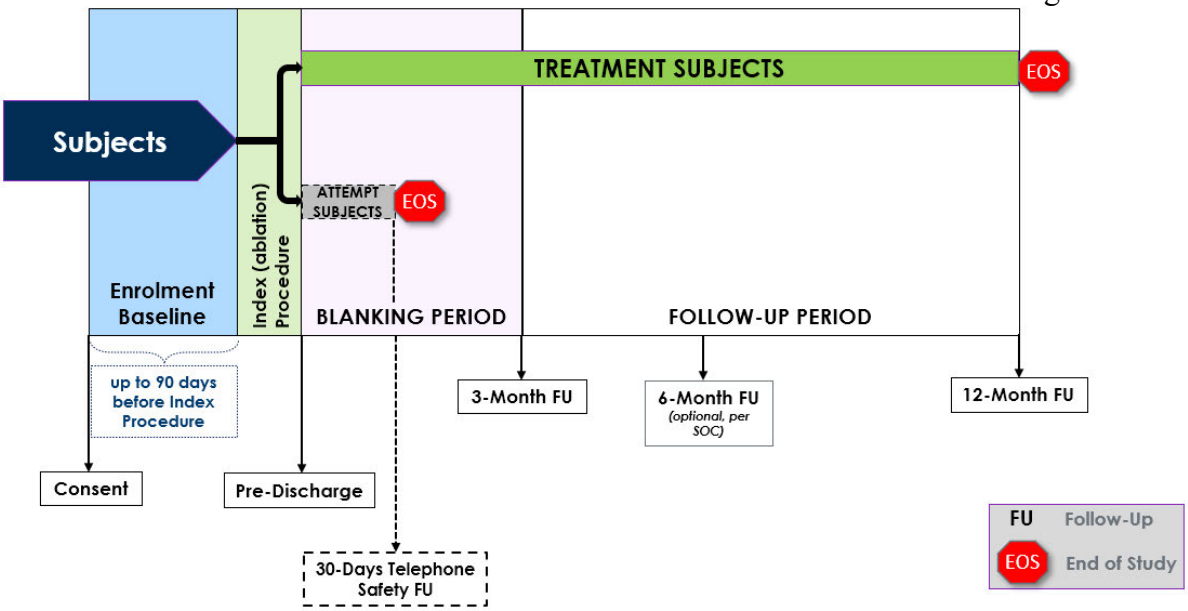

Figure 7.1-1: POLAR SMART Study Design

7.2. *Treatment Assignment*

All subjects who meet the eligibility criteria and sign the consent form will be considered enrolled in the study. Subjects will be classified based on subject status and classification (see Section 9.4).

7.3. *Justification for the Study Design*

According to the most recent guidelines, catheter ablation has deemed effective in restoring and maintaining sinus rhythm and reducing symptoms in subjects with symptomatic recurrent AF. The main goal of the study is to demonstrate the procedural success under real world conditions and document safety in a post market setting.

POLAR SMART is a prospective, multicenter, single arm, post-market study to collect real-world clinical data on safety, effectiveness and procedural success of Boston Scientific Cardiac Cryoablation System (POLARx^{TM} System) when use to perform PVI in the ablation treatment of De Novo AF.

The study is intended for collecting data in South Korea and Japan. Health care utilization, health economic and ethnic differences may have an impact on therapy in real world settings. PMCF data are helping to understand differences and equalities across patient cohorts from different enrollment regions and may support local guideline adjustments.

The subject population has been chosen based on clinically indication for PVI ablation procedure (in compliance with IFU / Tenpubunsyo as legally approved conditions). This study will collect real-world data on acute and chronic safety and effectiveness and extend the follow up to 12 months. In addition, adverse events will be collected through the follow-up period and will be compared to rates from literature

De novo subjects are selected where a cryoballoon will be used for first PVI. To determine the performance of the Cryoablation Balloon Catheter, an analysis of the ability to electrically isolate a targeted PV acutely will be completed. PVI measurements will be taken post cryo application to assess entrance block at the minimum.

In comparison to available alternative systems, the novel POLARx™ showed similar safety and efficacy compared to the Medtronic fourth generation of arctic front cryoballoon (AF-CB4). A higher rate of real-time PV recordings and significantly lower minimal balloon temperatures were observed using the POLARx™ (20).

This study is further contributing to the PMCF data collection, mandated under MDR, on the "POLARx™ Cardiac Cryoablation Catheter System". This study protocol and procedures have been designed to minimize any study burden for study subjects, including the selection and training of investigators. Patients may benefit from more advanced technology which is especially focused on procedure success and timing.

This study will also allow to capture roof-line ablations as part of prophylactic treatment in addition to PVI. This additional ablation has increasing importance in Japanese daily clinical routine. It is unknown to what extend these techniques are used and how those are impacting safety and efficacy of Cryoablation based PVI only. This study will allow an increased sample size in order to provide information on changes in clinical practice when PVI Cryoablation is used in combination with roof line ablation.

8. Subject Selection

8.1. *Study Population and Eligibility*

Subjects enrolled in this POLAR SMART study will be clinically indicated for PVI ablation procedure (in compliance with IFU/Tenpubunsyo as legally approved conditions) for the treatment of paroxysmal AF.

Subjects have to 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 criteria (see Table 8.2-1) may be given consideration for inclusion in this clinical investigation, provided no exclusion criterion (see Section 8.3) is met.

Table 8.2-1: Inclusion Criteria

Inclusion Criteria	1. Subjects indicated for the treatment of AF with the cryoablation system; 2. Subjects who are willing and capable of providing informed consent; 3. Subjects who are willing and capable of participating in all testing associated with this clinical study at an approved clinical investigational center; 4. Subjects who are of legal age to give informed consent specific to the national law.

8.3. *Exclusion Criteria*

Subjects who meet any one of the following criteria (Table 8.3-1) cannot be included in this study or will be excluded from this clinical study.

Table 8.3-1: Exclusion Criteria

Exclusion Criteria	1. Any known contraindication to an AF ablation or anticoagulation, including those listed in the IFU/Tenpubunsyo as legally approved conditions; 2. Any prior LA ablation; 3. AF secondary to electrolyte imbalance, thyroid disease, or any other reversible or non-cardiac cause; 4. Known or pre-existing severe PV Stenosis; 5. Evidence of cardiac myxoma, LA thrombus or intracardiac mural thrombus; 6. Previous cardiac surgery (e.g. ventriculotomy or atriotomy, CABG, PTCA, PCI, ventricular fistula or atrial incision) and any surgery within 90 days prior to enrollment; 7. Any implanted cardiac device (e.g. PM, ICD, CRT, valve replacement, LAAO, etc) within 90 days prior to enrollment; 8. Any planned OR scheduled cardiac device procedure (e.g. PM, ICD, CRT, valve replacement, LAAO, etc) during and post PVI ablation (during and post-index procedure); 9. Any planned ablation in LA except PVI procedure and roof line ablation; 10. Any planned ablation in ventricles; 11. Subjects undergoing atrial septal defect patch or other surgical procedures at or near the atrial septal defect; 12. Subjects with severe valvular disease OR with a prosthetic – mechanical or biological - heart valve (not including valve repair and annular rings); 13. Presence of any pulmonary vein stents; 14. Subjects with active systemic infection; 15. Subjects that have vena cava embolic protection filter devices and/or known femoral thrombus; 16. Any previous history of cryoglobulinemia; 17. Subjects that are unable to undergo atrium access safely or operate in the atrium as per investigator's medical judgement; 18. Subjects with no vascular access or obstruction of the femoral vein; 19. Subjects with blood coagulation disorders or diseases; 20. Any prior history of documented cerebral infarct, TIA or systemic embolism (excluding a post-operative DVT) ≤ 180 days prior to enrollment; 21. Subjects who are hemodynamically unstable;

Exclusion Criteria	22. Subject is unable or not willing to complete follow-up visits and examination for the duration of the study; 23. Subjects with life expectancy ≤ 1 year per investigator's medical judgement; 24. Women of childbearing potential who are, or plan to become, pregnant during the time of the study (assessment per investigator's discretion); 25. Subjects with unrecovered/unresolved AEs from any previous invasive procedure; 26. Subjects who are currently enrolled in another investigational study or registry that would directly interfere with POLAR SMART study. Exception 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 for approval.

9. Subject Accountability

9.1. *Point of Enrollment*

Investigators will select subjects who are appropriate for study inclusion as per eligibility criteria as specified under section 8.2 and 8.3. Subjects who have given written informed consent are considered enrolled in the study. No protocol-related activities can take place or no data from the subject can be collected until the Informed Consent Form (ICF) is signed and dated by the subject. Screening tests that are part of SOC can be used to determine pre-eligibility. Data from examination 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 investigator's site responsibility to assess eligibility criteria before obtaining the ICF.

9.2. *Withdrawal*

All subjects enrolled in the clinical study (including those withdrawn from the clinical study) shall be accounted for and documented. If a subject withdraws from the clinical investigation, the reason(s) shall be reported. If such withdrawal is due to problems related to device safety or performance, the investigator shall ask for the subject's permission to follow his/her status/condition as standard of care practice. Withdrawn subjects will not be replaced.

Reasons for withdrawal include but are not limited to physician discretion, change in inclusion/exclusion status, subject choice to withdraw consent, lost to follow-up, or death. While study withdrawal is discouraged, subjects may withdraw from the study at any time, with or without reason, and without prejudice to further treatment. All applicable case report forms up to the point of subject withdrawal and a "End of Study" form must be completed.

Every effort should be made to obtain full information on any ongoing reportable adverse events up to the point of withdrawal. All open reportable adverse events should be closed or documented as chronic. Data collected up to the point of subject withdrawal may be used,

unless any local regulations apply. Additional data may no longer be collected after the point at which a subject has been withdrawn from the study or withdraws his/her consent, for whatever reason.

9.3. *Lost to Follow-Up*

A subject will be considered lost to follow-up if he/she fails to return to scheduled visits as per Data Collection Schedule (Table 10.1-1), and is unable to be contacted by the study site staff.

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 to 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 (3 attempts, including telephone calls and/or a certified letter to the participant's last known mailing address or local equivalent methods, where possible). These contact attempts must be documented in the subject's medical record or study file and in the "End of Study" Electronic Case Report Forms (eCRFs).
- Should the subject continue to be unreachable, he or she will be considered lost to follow-up from the study.

9.4. *Subject Status and Classification*

9.4.1. Consent Ineligible (Screening Failures)

A subject who has given written informed consent but is found not to meet eligibility criteria before undergoing the index procedure and before having the study device inserted in the body, will be classified as "Consent Ineligible".

Subjects determined to be Consent Ineligible do not count towards the enrollment ceiling and will not be used for analysis of the endpoints. The original signed and dated ICF must be maintained in the center's subject file. A subject identification number (ID) will be assigned in the Electronic Data Capture (EDC) system.

For consent ineligible subjects, at the minimum the following forms must be completed:

- Enrollment eCRFs;
- Adverse Event eCRFs for any reportable event (as defined in section 17) that occurs after signing the ICF, up to the point of subject withdrawal;
- Protocol deviation eCRF, if applicable;
- End of Study eCRF.

9.4.2. Intent

A subject who has given written informed consent, meets eligibility criteria, but does not have any study devices inserted into the body will be classified as "INTENT". This includes subjects that had been prepared for the procedure (e.g. medication administered) and/or who had non-study devices inserted into the body. Subjects that are enrolled in the study but do not undergo ablation procedure within 90 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 towards the enrollment ceiling and will not be used for analysis of the endpoints. The original signed ICF must be maintained in the center's subject file. A subject ID will be assigned in the EDC system.

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

- Enrollment and Baseline eCRFs;
- Adverse Event eCRFs for any reportable event (as defined in section 17) that occurs after signing the ICF, up to the point of subject withdrawal;
- Protocol deviation eCRF, if applicable;
- End of Study eCRF.

9.4.3. Attempt

A subject who has given written informed consent, and has any study device inserted into the body but does not receive any Cryoablation application will be classified as "ATTEMPT." Attempts subjects will count towards the overall enrollment ceiling of 400 subjects and will be used for analysis of the endpoints as per section 11.2.1. The original signed ICF must be maintained in the center's subject file. A subject ID will be assigned in the EDC system. These subjects won't be allowed to be re-enrolled in the study.

Attempt subjects will be followed up to 30 days after index procedure, for safety purposes. All applicable case report forms in the EDC system will be completed. The original signed Informed Consent and any relevant documentation must be maintained in the center's subject file.

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

- Enrollment and Baseline eCRFs;
- Index Procedure eCRFs;
- 30 days Safety follow-up Phone Call;
- Adverse Event eCRFs or Device Deficiency eCRF for any reportable event (as defined in section 17) that occurs after signing the ICF, up to the point of subject withdrawal;
- Protocol deviation eCRF, if applicable;
- End of study eCRF.

9.4.4. Treatment

Any subject who has given written informed consent and has the specified study device inserted into the body and received at least one Cryoablation application will be classified as "TREATMENT". These subjects are followed in accordance with the Data Collection Schedule (Table 10.1-1) and included in all study analyses. A subject ID will be assigned in the EDC system. For TREATMENT subjects, all applicable eCRFs per the protocol will be completed. Treatment subjects do count towards the overall enrollment ceiling and will be used for analyses of the endpoints. The original signed ICF and any relevant documentation must be maintained in the center's subject file. Treatments will be further classified into the following subgroups:

- **PVI-only**: Subjects receiving treatment for PVI only or PVI and CTI.
- **PVI plus additional ablations (PVI+)**: Subjects receiving treatment for PVI (or PVI and CTI), plus additional ablations at other anatomical location(s) in the right or left atrium intended to treat AF, AT or atypical AFL.

PVI-only subjects are included in all study analyses, with additional primary endpoint analyses being performed for PVI+ subjects as well as combined PVI-only and PVI+ subjects, as described in Section 11.2.1.

9.5. *End-of-Study Definition*

The clinical study is considered completed when subjects are no longer being examined or the last subject's last study visit has occurred. The subject's end of study is defined as completion of the last visit or procedure as shown in the Data Collection Schedule (Table 10.1-1) in the study.

10. Study Methods

10.1. *Data Collection*

The data collection schedule is shown in Table 10.1-1. Data collection will take place at the following time points:

- Informed Consent and Enrollment clinic visit
- Baseline clinic visit, can be the same day as enrollment visit, however the Informed Consent must be signed and dated prior to conducting any study related activities (up to 90 days before Index Procedure);
- Index (Ablation) procedure (day 0);
- Pre-discharge visit must be done before hospital discharge (required);
- 3 months follow-up visit (recommended in-clinic follow-up visit if done as per SOC, at a minimum a telephone contact follow-up is required.) This telephone contact follow-up would only be required if in-clinic follow-up was not done.

- 6 months follow-up visit (optional, this can be either a in-clinic follow-up visit or a telephone contact follow-up as per SOC.);
- 12 months in-clinic follow-up visit (required);
- An additional follow-up visit is any subject visit triggered by subject symptoms, clinical events or per SOC that is not already defined as one of the study visits at the investigational site.

Table 10.1-1: Data Collection Schedule

Procedure/Assessment	**Enrollment Baseline**[2]	**Index (ablation) Procedure** Day 0	**Prehospital Discharge** Post-Procedure before discharge	**Month 3 Follow-Up** (91±14 days) *Clinic visit / Telephone*	**Month 6 Follow-Up** (180±30 days) *Clinic visit / Telephone*	**Month 12 Follow-Up** (365±40 days) *Clinic visit*	**Additional Follow-Up**	**Repeat (additional) ablation procedure**	**30-Days Safety Telephone Follow-Up** *(for attempt subjects only)*
Informed consent process, including informed consent signature date[1]	X								
Eligibility criteria	X								
Demographics	X								
Medical history	X								
LVEF, LA diameter and LA volume	SOC[3]								
Physical assessment	X		X	SOC	SOC	X	SOC		
LA assessment[5] **imaging and thrombus assessment**	SOC[4]								
Quality of Life (AFEQT and EQ-5D-5L)	X					X			
Procedural Data		X						X[9]	
3D Mapping information		SOC							
12-Lead ECG	X[6]	X	SOC	SOC	SOC	X	SOC	X	
Documentation of intervention for AF/AF/AT (if any)			X	X	X	X	X	X	
Documentation of new AF/AFL/AT (if any)		X	X	X	X	X	X	X	
Documentation of Medications	X	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	
Protocol deviations	X								
Adverse events assessment	X[8]								

X = required; SOC – reporting required if done per standard of care;

[1] Informed Consent must be signed and dated prior to conducting any study related activities (up to 90 days before Index Procedure).
[2] Baseline visit can be the same day as enrollment visit, however the ICF must be signed before any study-related activities.
[3] Per investigator's method. It is recommended to have the assessment within 180 days prior to enrollment.
[4] Assessment of left atrium anatomy, pulmonary veins anatomy and rule-out presence of thrombus is strongly recommended and to be performed according to site's SOC practice - Assessments can be performed using CT, Magnetic Resonance Imaging (MRI), pulmonary venogram, Intracardiac Echo (ICE), Trans-Esophageal Echocardiography (TEE) or other.
[5] It is recommended to have the LA assessment performed within 180 days prior to enrollment.
[6] Most recent rhythm via 12-lead ECG.
[7] Data will be required if there is any New, discontinued or changes to current Anti-Arrhythmic Drugs and Anticoagulation medication regimen.
[8] Adverse event assessment will be performed as from enrollment until study completion.
[9] Procedural data required for this visit is minimum, refer to protocol section 10.11 for details.

10.2. *Study Candidate Screening*

Investigators are responsible for screening all subjects and selecting those subjects who are appropriate for study inclusion, as per eligibility criteria (see section 8).

The subjects selected for participation should be from the investigator's general patient population. The investigator is expected to follow hospitals SOC testing to diagnose and screen subjects for inclusion in the study.

Prior to having any study related activities performed, subjects must give written informed consent to the study, as per section 10.3 and section 18.

10.3. *Informed Consent and Enrollment*

Subjects who provide written informed consent are considered enrolled in the study. As soon as informed consent is obtained, subject's eligibility criteria can be determined. A qualified center representative will review the consent with a potential subject. The subject should be given ample time to consider participation and ask questions if necessary. All questions from the subject should be addressed prior to the subject signing the ICF. An approved ICF shall be signed and dated by the subject. After the subject signs the ICF, a signed copy must be provided to the subject and the original is to be filed in the electronic or paper medical records. No study-specific data collection of any procedure should be conducted prior to consent.

The index procedure must be performed within 90 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 9.4.2). The intent subject cannot be re-enrolled as re-enrollment is not allowed in this study. The site will ensure that originally signed ICF and documentation of the ICF signature process are filed in subjects' files and that the subject's participation into the study is documented per hospital process (e.g.in the medical file). Original signed ICFs and the ICF process documentation will be made available for review at Monitoring Visits.

For additional information regarding the informed consent process, refer to section 18.

10.4. *Baseline Visit*

The following assessments must be performed during the baseline visit. Baseline visit can be the same day as enrollment visit, however the ICF must be signed and dated prior to conducting any study related activities (up to 90 days before Index Procedure). These assessments shall be recorded on the respective eCRF.

- Visit date;
- Documentation of ICF signature date;
- Eligibility criteria check;
- Demographics – including age at time of consent, gender;
- Medical history – including, but not limited to:
    - Underlying Cardiovascular disease (if any) and history of cardiac events;
    - Arrhythmia history;

- Non-cardiac comorbidities;
- Prior surgical interventions and/or cardiac procedures.

- LVEF, left atrial diameter, left atrial volume (if available), as per investigator's method. It is recommended to have the assessment within 180 days prior to enrollment;
- Physical Assessment – including height, weight, resting heart rate, systolic and diastolic blood pressure;
- Quality of Life assessment through AFEQT and EQ-5D-5L questionnaires;
- Most recent rhythm via 12-lead ECG;
- Medications: Current Anti-Arrhythmic Drugs and Anticoagulation medication regimen;
- Protocol deviations, if applicable.

The assessment of LA anatomy* and the screening for potential LA thrombi prior to the procedure is strongly recommended to be performed according to the site's SOC practice, however it is recommended to follow the indications from the HRS/JCS consensus statement for AF ablation (1,14).

This includes :

- For check out presence of left atrial thrombus** and cardiac examination: The gold standard per JCS for diagnosis is TEE observation prior ablation.
- Alternatively Cardiac MRI, spiral CT scan, ICE or pulmonary venogram, to assess PV anatomy and PV dimension may be used.

*It is recommended to perform the LA anatomy assessment within 180 days prior to enrollment.

** If a thrombus is observed prior to ablation, the subject no longer meets eligibility criteria and shall not have the ablation procedure performed: the subject will then be withdrawn from the study, classified as Consent Ineligible and no further follow-up is required.

10.4.1. Medications

10.4.1.1. Anti-Arrhythmic Drugs

Information on all AAD medications will be collected on the eCRF starting from baseline visit. During the entire course of the study, details on changes will be specified on the eCRF. Post-index procedure AADs are allowed per investigator's discretion during the blanking period (90 days post-index procedure). According to HRS/JCS consensus guidelines (1,14), it is recommended to stop the administration of AAD for any AT after blanking period. If the investigator determines that the subject must be prescribed an increased dosage of AAD or a new AAD for treatment of any AT 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/AFL/AT recurrence.

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

10.4.1.2. Anticoagulation

The use of anticoagulation up to the procedure (including up to transseptal puncture) is per SOC of the investigator. Information on anticoagulation therapy, pre and post index procedure will be collected in the eCRF.

It is recommended that heparin is administered prior to or immediately following transseptal puncture during ablation procedure and adjusted to achieve and maintain an ACT of at least 300 seconds. The ACT levels should be checked at a 15-30 minutes interval during the duration of the procedure.

10.5. *Index (ablation) Procedure (Day 0)*

10.5.1. General Info

All subjects must meet the eligibility criteria prior to Index (ablation) Procedure. If subject is found not meeting eligibility criteria, it will be withdrawn from the study.

The study-related ablation procedure must be performed by study-delegated investigators trained in electrophysiology (EP). Any reportable safety events that occur must be reported on the Adverse Event eCRF. The index ablation procedure must be performed within 90 days of a subject's enrollment into the study.

10.5.1.1. Esophagus Management

Information on esophagus management, if any, will be collected in the eCRF (e.g. temperature monitoring, esophageal deviation). It is highly recommended to perform temperature monitoring.

10.5.1.2. Phrenic Nerve Activity Monitoring

During ablation, phrenic nerve activity monitoring will be performed according to the SOC at the site. In case of phrenic nerve injury at the procedure, the subject status and potential resolution of the adverse event will be monitored during the course of the study.

10.5.1.3. Pulmonary Vein Isolation

The goal of the ablation procedure is electrical isolation of all pulmonary veins or anatomical equivalents. Electrical isolation of the veins must be demonstrated at minimum with evidence of entrance block in all of the pulmonary veins using the Cryo Mapping Catheter (Other techniques of additional assessment are per investigator's discretion or as per SOC).

If the subject is in AF prior to the ablation, it will be up to the investigator's discretion whether to cardiovert or proceed with the procedure with the subject in AF. Electrocardiographic documentation of the subject's rhythm prior to ablation will be collected.

10.5.1.4. 3D mapping

Three-dimensional (3D) mapping may be used during the procedure. If 3D mapping is performed, a commercially available device will be used, and the information should be collected on the eCRF including: mapping catheter, 3D mapping system, mapping times etc.

In case a post PVI map is collected, information on lesion and/or presence of conduction gaps should be collected for each PV. Potential gaps or poor lesion extension will be collected including localization information: vein and anatomical location.

10.5.1.5. Cryoablation System Preparation

All devices must be prepared as described in the IFU / Tenpubunsyo.

The console will create a record for each ablation attempted, including (but not limited to) ablation duration and cryoballoon temperature. Esophagus temperature and DMS activity data will also be collected if esophageal probe and DMS are connected.

In order to accurately capture information relevant to the study, the following information must be entered into the Console at each index procedure:

Prior to ablation:

- On the subject information screen, enter the subject's identification (subject ID is provided by the EDC system when enrolling the subject) and the operating physician's name.
    - If the physician decides to use DMS it should be connected to the subject during right PV ablations (for data acquisition). The DMS is an adjunctive sensor designed to monitor a phrenic nerve pacing response. SOC methods for evaluating phrenic nerve function and determining when intervention is needed (e.g. palpation, ICE) should always be applied during right pulmonary vein ablations. The DMS is not intended as a substitute for such SOC methods.
    - In case the DMS is used, the steps reported in the IFU/Tenpubunsyo will be followed.

10.5.2. Cryoablation procedure steps

Preparation activities should be performed as follows:

1. Assessment of presenting rhythm by 12-lead ECG.
2. Baseline the fluoroscopy exposure time (Time 0).
3. Place additional diagnostic catheters, for example in the coronary sinus or for pacing the phrenic nerve, at the discretion of the physician.
4. Per institutional protocol, complete transseptal access (single or double).
5. Prepare the Cryo Steerable Sheath. Insert the sheath over the guidewire and advance the sheath across the atrial septum.
6. Prepare the Cryoablation Catheter and the Cryo Mapping Catheter. Insert the Cryo Mapping Catheter into the Cryoablation Catheter. Insert the Cryoablation Catheter into the Cryo Steerable sheath and advance it into the left atrium.

7. Baseline the LA dwell time.

Following the step-wise approach for the ablation procedure is recommended:

8. Navigating and positioning of the balloon
    a. Advance the Cryo Mapping Catheter and Cryoablation Catheter under fluoroscopic guidance to the proximity of the target PV
    b. Inflate the balloon while remaining outside of the target PV
    c. Occlude targeted vein by advancing the balloon as necessary but remain outside of the tubular portion of the vein.
    d. Verify balloon position of the PV occlusion. Verification may be performed with fluoroscopy and/or contrast injection or other technique (per investigator's discretion).
    e. If the selected vessel is a right PV, start phrenic nerve pacing prior to starting the cryoablation.
9. Cryo Ablation of all target PVs
    a. Perform cryo ablation. A minimum ablation time of TTI + 120sec is highly recommended, where possible. If no PV potential is visible, a minimum ablation time of 180sec is highly recommended.
    b. During each ablation application: annotate the anatomical location of ablation, the time-to-isolation* (as observed on the PolarMap EGMs and representing the time point when electrical activity disappears) and the ablation duration.

        * TTI is required to be captured through the console, when available.

    c. Wait for the thawing phase to be completed prior to manipulating the Cryoablation Catheter.
    d. As needed, perform additional cryoablation in the same PV, adjusting the position of the Cryoablation Catheter, if necessary.
10. Confirmation of isolation of the PV at minimum by entrance block using the Cryo Mapping Catheter (Other techniques of additional assessment are per investigator's discretion) is required for all pulmonary veins or their anatomical equivalent.

Note: If at any time during the ablation procedure, the investigator is unable to continue the ablation with the designated study catheter (for the PV isolation), the investigator may complete the case with a device determined best for the subject. The case will represent an acute procedural failure (per protocol definition), regardless of PVI achievement with other catheters. The point at which failure was determined as well as the rationale (including a device deficiency or adverse event, if any) must be documented in the EDC system. A protocol deviation will be documented in the EDC system.

10.5.2.1. Cryoablation-specific recommendations

Investigators may deliver one or more cryo applications per each pulmonary vein (or their anatomical equivalent) in order to achieve PVI.

In order to preserve subject's safety, it is recommended to adhere to the following indications:

- Terminate ablation if, in case of temperature monitoring, esophagus temperature falls below 20°C. Do not start a 2nd ablation until esophagus temperature returns to baseline levels.
- Terminate ablation if an impairment of diaphragmatic movement is detected by the operating investigator during ablation. Do not start a 2nd ablation until phrenic nerve activity returns to baseline levels.
- Do not apply more than 2 consecutive ablations in the same PV location if applicable*
- Do not apply more than 4 total ablations in a single PV*

* Ablations inferior to 60 seconds in duration are not considered in the total ablation count. Multiple ablations superior to these recommended numbers are reasonable in case of segmental ablations of large common trunk.

10.5.3. Additional ablation(s)

The Cryoablation System cannot be used for the ablation of other arrhythmia(s)/additional line(s) or applications outside the PVs. For this purpose another commercially available ablation system will be used. If additional ablations are required, BSC recommends performing the PVI first and at minimum by entrance block testing.

Additional ablations outside PVs could be done:

- In the right atrium per physician's discretion (including but not limited to CTI lines for treatment of atrial flutter).
- In the left atrium:
  - Roof line ablations are accepted if those are part of SOC during PVI ablation procedures.
  - To complete any unsuccessful PV isolation that may occur.
  - To treat any emergent arrhythmia (spontaneous or induced) that would require treatment for patient welfare. Ablations in the left atrium with another commercially available catheter to complete any unsuccessful PV isolation that may occur or to treat any emergent arrhythmia (spontaneous or induced) that would require treatment for patient welfare.

Additional ablations outside PVI cannot be done:

- In the left atrium:
  - Posterior wall and any other ablations are not accepted under this protocol.
  - Any advance planned ablations outside PV, if not triggered by an emergent arrhythmia (spontaneous or induced).
- Any scheduled ventricular ablations.

If the subject presents with AF after all ablations are complete, cardioversion should be performed and will be noted. Cardioversions during the Index procedure do not signify procedural failures and are not to be reported as adverse events. Induction of or spontaneous conversion to AF during the procedure will not be considered an adverse event.

10.5.4. Index Procedure Data Collection

The following data ***related to the procedure*** will be collected:

- Date of procedure
- Identification of study devices for the following:
    - Cryoablation Catheter
    - Cryo Mapping Catheter
    - Cryo Steerable Sheath
    - Console
    - Related accessories
- Identification of non-study devices (if applicable):
    - Any additional sheaths/introducers used during the procedure including manufacturer, model and type
    - Any additional catheter(s) used during the procedure including manufacturer, model, and type (e.g. Coronary Sinus (CS) catheter)
    - Mapping system, if used (manufacturer, model and software version)
- Presenting rhythm at the beginning of the procedure (by means of a 12-lead ECG)
- Method of delivering sedation or anesthesia for the procedure
- Method of transseptal access to left atrium: single or double
- Method of evaluating phrenic nerve function and determining when intervention is needed

Specific to the ***PVI ablation*** the following information will be collected (including, but not limited to):

- Per each ablation application:
    - Acute Time-to-Isolation (if available)
    - Minimum balloon temperature
    - Time to thaw
    - Duration of each cryo application
    - DMS and Esophageal temperature, if available
    - Reason, if any, for premature interruption of the ablation
- For each pulmonary vein or anatomical equivalent:
    - PV isolation success, at minimum by entrance block using the Cryo Mapping Catheter (Other techniques of additional assessment are per investigator's discretion) documented through EGMs printed from recording system and/or in medical file.

- Any other ablation performed during the index procedure (before, during or after PVI)

At the ***end of the procedure***, the following information will be collected:

- Total procedure time, defined as time elapsed from time first access sheath insertion into the subject until the last catheter removed;
- Total Fluoroscopy time measured from baseline fluoroscopy time (Time 0);
- Total cryoablation time (duration of all cryo applications);
- Duration of LA dwell time, defined as time from the Cryoablation Catheter introduced in the LA (exiting the sheath) to the last time of Cryoablation Catheter exiting the LA;
- Rhythm at end of case (documented by means of a post-ablation EGM/12-lead ECG);
- Cardioversion(s) performed during the procedure, if any;
- Assessment of reportable adverse events including resolution of ongoing events, if applicable/ device deficiencies;
- Assessment of phrenic nerve palsy (method per investigator's discretion, eg. through fluoroscopy of diaphragm movement);*
- Protocol deviations, if applicable.

**Subjects may be intubated or not breathing spontaneously at the conclusion of the procedure, which may impair appropriate assessment of phrenic nerve functionality. Therefore, at the discretion of the investigator, it is recommended that pacing of the phrenic nerve to be performed using an intracardiac catheter during the required post-ablation fluoroscopy to observe diaphragm movement and assess for phrenic nerve palsy. If abnormality is detected during post-ablation testing, it is recommended to follow-up according to standard of care for phrenic nerve palsy. Additionally, a similar pre-ablation assessment of the subject for phrenic nerve palsy is encouraged as a baseline comparator*

The ablation data report collected through the console will be saved and exported to external media, as provided by the sponsor.

10.6. *Pre-Discharge*

The pre-discharge follow-up visit must be completed before the subject is discharged from the hospital.

Data collection during the Pre-Discharge visit will be recorded on the respective eCRF.

Data collection includes:

- Date of visit;
- Physical assessment including at minimum resting heart rate, weight, systolic and diastolic blood pressure;
- Rhythm at time of visit (by means of a 12-lead ECG) if available;

- Any documented recurrent AF episode(s), or new onset of AFL or AT events (≥ 30 seconds in duration from any clinical recording devices or from a 10-second 12-lead ECG);
- Any of the following interventions for AF, or new onset of AFL or ATs;
    - Repeat procedure
    - Electrical and/or pharmacological cardioversion for AF/AFL/AT
- New, discontinued or changes to current Anti-Arrhythmic Drugs and Anticoagulation medication regimen;
- Protocol deviations, if applicable;
- Reportable Adverse Events, including resolution of ongoing events, if applicable.
    - In cases of phrenic nerve palsy at the index procedure, the subject should be assessed to evaluate if the event resolved (method per investigator's discretion).

10.7. *Month 3 Follow-up (91 ± 14 days)*

The Month 3 follow-up must be completed between 77 and 105 days post-index procedure.

Month 3 follow-up visit: recommended in-clinic follow-up visit if done as per SOC at a minimum a telephone contact follow-up is required. This telephone contact follow-up would only be required if in-clinic follow-up was not done. Due to the range for the visit completion and the endpoint requirement for medication, AAD medication changes made during the Month 3 Follow-up visit will be counted as being made within the blanking period.

Data collection during the Month 3 follow-up visit will be recorded on the respective eCRF.

Data collection includes:

- Date of visit/telephone;
- Physical assessment including at minimum resting heart rate, weight, systolic and diastolic blood pressure (not required for telephone);
- Any documented recurrent AF episode(s), or new onset of AFL or AT events (≥ 30 seconds in duration from any clinical recording devices or from a 10-second 12-lead ECG);
- Any of the following interventions for AF, or new onset of AFL or ATs;
    - Repeat procedure
    - Electrical and/or pharmacological cardioversion for AF/AFL/AT
- New, discontinued or changes to current Anti-Arrhythmic Drugs and Anticoagulation medication regimen;
- Protocol deviations, if any;
- Reportable Adverse Events, including resolution of ongoing events, if applicable.

- In cases of a pre-existing and unresolved phrenic nerve palsy the subject should be assessed to evaluate if the event resolved (method per investigator's discretion).

10.8. *Month 6 Follow-up (180 ± 30 days)*

Month 6 follow-up visit is optional, this can be either a in-clinic follow-up visit or a telephone contact follow-up as per SOC.

If any SOC clinical visit is completed either in clinic or telephone call between 150 and 210 days post-index procedure, it will qualify as a Month 6 follow-up.

Data collection during the Month 6 follow-up visit will be recorded on the respective eCRF.

Data collection includes

- Date of visit/telephone;
- Physical assessment including at minimum resting heart rate, weight, systolic and diastolic blood pressure (not required for telephone);
- Any documented recurrent AF episode(s), or new onset of AFL or AT events (≥ 30 seconds in duration from any clinical recording devices or from a 10-second 12-lead ECG);
- Any of the following interventions for AF, or new onset of AFL or ATs;
  - Repeat procedure
  - Electrical and/or pharmacological cardioversion for AF/AFL/AT
- New, discontinued or changes to current Anti-Arrhythmic Drugs and Anticoagulation medication regimen;
- Protocol deviations, if any;
- Reportable Adverse Events, including resolution of ongoing events, if applicable.
  - In cases of a pre-existing and unresolved phrenic nerve palsy the subject should be assessed to evaluate if the event resolved (method per investigator's discretion).

10.9. *Month 12 Follow-up Visit (365 ± 40 days)*

The Month 12 follow-up must be completed between 325 and 405 days post-index procedure, in-clinc visit is required.

Data collection during the Month 12 follow-up visit will be recorded on the respective eCRF.

Data collection includes

- Date of visit;
- Physical assessment including at minimum resting heart rate, weight, systolic and diastolic blood pressure;
- Quality of Life assessment through AFEQT and EQ-5D-5L questionnaires;

- Rhythm at time of visit (by means of a 12-lead ECG);
- Any documented recurrent AF episode(s), or new onset of AFL or AT events (≥ 30 seconds in duration from any clinical recording devices or from a 10-second 12-lead ECG);
- Any of the following interventions for AF, or new onset of AFL or ATs;
    - Repeat procedure
    - Electrical and/or pharmacological cardioversion for AF/AFL/AT
- New, discontinued or changes to current Anti-Arrhythmic Drugs and Anticoagulation medication regimen;
- Protocol deviations, if any;
- Reportable Adverse Events, including resolution of ongoing events, if applicable.
    - In cases of a pre-existing and unresolved phrenic nerve palsy the subject should be assessed to evaluate if the event resolved (method per investigator's discretion).

10.10. *Additional Visits*

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

Data collection during the additional follow-up visit will be recorded on the respective eCRF.

Data collection should include:

- Date of visit;
- Physical assessment including at minimum resting heart rate, weight, systolic and diastolic blood pressure;
- Any documented recurrent AF episode(s), or new onset of AFL or AT events (≥ 30 seconds in duration from any clinical recording devices or from a 10-second 12-lead ECG);
- Any of the following interventions for AF, or new onset of AFL or ATs;
    - Repeat procedure
    - Electrical and/or pharmacological cardioversion for AF/AFL/AT
- New, discontinued or changes to current Anti-Arrhythmic Drugs and Anticoagulation medication regimen;
- Protocol deviations, if any;
- Reportable Adverse Events, including resolution of ongoing events, if applicable.
    - In cases of a pre-existing and unresolved phrenic nerve palsy the subject should be assessed to evaluate if the event resolved (method per investigator's discretion).

10.11. *Repeat ablation procedure*

It is known that during the first 90 days post-index procedure (blanking period), subjects can suffer from recurrences of AF or onset of new AT. Within the blanking period, more than one repeat ablation procedure, using a commercially available ablation system, is allowed.

A repeat ablation procedure performed after blanking period will count as a failure for the primary effectiveness endpoint. During the repeat ablation procedure, the anatomical location of potential ablation gaps in the pulmonary veins will be assessed.

In case a repeat ablation procedure occurs during the 12 month follow-up period, the data of this procedure will be entered in the 'Additional Procedure' eCRF. In case this ablation procedure is performed to treat a supraventricular arrhythmia, including AF, AFL or AT, following detailed information about this repeat ablation procedure will be collected:

- Was the ablation procedure performed in the LA?;
- Was this repeat ablation procedure performed using BSC cryoablation?;
- For repeat ablation procedures performed in the LA: was this repeat ablation procedure performed to treat AF/AFL/AT? If no, specify the arrhythmia type;
- Rhythm at the beginning (12-lead ECG) and the end of the repeat procedure (documented by means of a post-ablation EGM/12-lead ECG);
- Reportable Adverse Events, including resolution of ongoing events, if applicable, and/or Device Deficiencies;
    - In cases of a pre-existing and unresolved phrenic nerve palsy the subject should be assessed to evaluate if the event resolved (method per investigator's discretion);
- Protocol deviations, if applicable.

10.12. *Study Completion*

All TREATMENT subjects will be followed for 12 months after the index (ablation) procedure. Data collection will continue up to the point of the Month 12 close out follow-up visit. The End of Study eCRF will have to be completed at study completion.

10.13. *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. monsoons, typhoons, earthquakes, snow storms, floods etc.) 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/AFL/AT. Any

clinical recording devices as long as the requirements listed in this protocol are fulfilled (e.g. 24-hour Holter monitoring, home monitoring systems or implanted devices) can be used to detect any recurrence of AF/AFL/AT.

10.14. *Source Documents*

It is preferable that original source documents are maintained, when available. In lieu of original source documents, certified copies are required to be maintained. A certified copy is a copy (irrespective of the type of media used) of the original record that has been verified (i.e., by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original. Source documentation includes but is not limited to those items noted in Table 10.14-1.

Table 10.14-1: Source Documentation Requirements

Requirement	Disposition
Informed Consent documentation process	Retain at Center
Medical history documents pertaining to eligibility criteria	Retain at Center
Documentation of demographics data	Retain at Center
Physical assessment	Retain at Center
Medication regimen and Changes	Retain at Center
Medical history	Retain at Center
Quality of Life Instruments (AFEQT and EQ-5D-5L)	Retain at Center
Documentation of isolation confirmation for each Pulmonary Vein	Retain at Center
Printed and signed PDF Console Export Case Data	Retain in subject binder
12-Lead ECGs data including ongoing rhythm	Retain at Center
Signed Technical Source Form	Retain in subject binder
Imaging, per SOC at the site	Retain at Center
Documentation of new AF/AFL/AT AND Intervention for AF/AFL/AT	Retain at Center
Adverse Events	Retain at Center
In the event of a subject death (if requested): • Death narrative • Relevant medical records • Death Certificate • Autopsy report	Submit one copy to BSC, Retain one copy at center

11. Statistical Considerations

Statistical considerations for the primary and secondary endpoints are described in the following sections. Note that no formal hypothesis tests are planned for the endpoints.

11.1. *Endpoints*

11.1.1. Primary Safety and Effectiveness Endpoints

11.1.1.1. Statistical Methods

The 12-month (365-day) event/failure-free rates 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 withdrawal. The corresponding 2-sided 95% confidence limits will be calculated as the pointwise confidence limits using the log-log methodology.

[redacted]

11.1.2. Secondary Endpoints

Acute procedural success:

The percentage of Treatment subjects achieving acute procedural success will be calculated, along with the corresponding 95% 2-sided Clopper-Pearson confidence interval.

Failure-free rate at 6 months post-index procedure:

The 6-month (183-day) event/failure-free rates will be calculated using Kaplan-Meier methodology. Subjects who withdraw from the study prior to 6 months without experiencing an event will be censored on the date of withdrawal. The corresponding 2-sided 95% confidence limits will be calculated as the pointwise confidence limits using the log-log methodology.

11.2. *General Statistical Methods*

Time-to-event endpoints will be summarized using Kaplan-Meier event-free rates with 2-sided 95% pointwise log-log confidence limits. Subjects who withdraw from the study prior to 12 months without experiencing an event will be censored on the date of withdrawal.

Summary statistics will be presented for secondary and additional endpoints. E.g. event rates and confidence intervals will be provided for binary endpoints, and mean ± SD and/or min, max, and median and quartiles will be presented for continuous endpoints.

11.2.1. Analysis Sets

The main analyses for all endpoints will be limited to PVI-only subjects . All available data from these subjects will be utilized. An additional summary of acute primary safety endpoint results (per Section 6.2.1) and adverse events will be provided for all Attempt subjects. Also, additional endpoint analyses may be performed on all Treatment subjects, subjects treated

with a POLARx™ FIT device, as well as subgroups of subjects who did have additional ablations beyond PVI. These subgroups include, but are not limited to:

- Subjects undergoing CTI
- Subjects undergoing CTI and other RA ablations
- Subjects undergoing LA ablations beyond just PVI.

11.2.2. Control of Systematic Error/Bias

Selection of subjects will be made from the investigator's population. All subjects that have signed the ICF will be enrolled in the study.

11.2.3. Number of Subjects per Investigative Site

To avoid any center effect and bias, individual centers will not be allowed to enroll more than 20 subjects meeting enrollment criteria, unless Boston Scientific gives written approval to do so. Enrollment of an amount of study subjects in excess of such approved number of 20 total subjects must first be approved by sponsor, notified/submitted to Institution's IRB/EC, as applicable, and requires an amendment of exhibit A of the clinical study agreement.

11.3 Data Analyses

11.3.1. Interim Analyses

No formal interim analyses are planned for the purpose of stopping the study early for declaring effectiveness or for futility. Analysis of each endpoint will be performed when all applicable data for that endpoint has been collected. Analyses of acute data (procedural safety and acute procedural success) may be performed and used for publication purposes after completion of study enrollment, index procedure, 7 day and 3 month follow-up of all subjects.

11.3.2. Subgroup Analyses

Additional ancillary analyses on specific subgroup of subjects, may be presented.

These analyses will include but not limited to the following:

- Age (< 60 versus ≥ 60 years);
- Gender (Male versus Female);
- Monitoring (Subjects with data from continuous ECG recording systems (eg. ILR, PM, ICD, CRT) versus those without).

11.3.3. Justification of Pooling

Center-to-center heterogeneity will be assessed for the primary endpoints by performing a random effects logistic regression analysis. Centers with less than five enrollments will be combined to form "supercenters". Small centers will be combined until the newly created supercenter has five enrollments, and then a new supercenter will be created. Centers will be

deemed to be heterogeneous if the variance of the random center effect is found to significantly differ from zero. A significance level of 15% will be used for this test.

11.3.4. 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.

The analysis will be done for the entire study cohort as well as for the following treatment cohorts:

- PVI-only subjects
- PVI+ subjects
- Subjects treated with the POLARx™ FIT device

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)
- Procedural techniques (e.g., esophageal temperature monitoring,)

Additional multivariable analyses will be performed to assess on the effect of cryo dosing parameters on acute (e.g. procedure duration, dwell time, acute success, acute adverse events, and other procedural outcomes) and chronic parameters e.g. (freedom from effectiveness failure). Analyses will be performed on a per-subject and per-vein basis. Cryo dosing parameters to be assessed for use in the per-subject model may include, but not be limited to:

- Total number of applications > 60s
- Total application duration.

Cryo dosing parameters to be assessed for use in the per -vein model may include, but not be limited to:

- Total number of applications > 60s
- Total application duration.
- Occlusion score
- TTI driven applications (yes or no)
- TTI.

11.3.5. Additional Analyses

Additional analyses include, but are not limited to:

- Procedure times: LA dwell time*, total ablation time, number of cryo applications per vein, time to thaw, total fluoroscopy time and total procedure time;
- Time-To-Isolation per ablation application, if available;

- Freedom from recurrence of individual types of AF, or new AFLs or ATs between Days 91 and 12-month follow-up;
- Analysis of additional ablation techniques performed as there is foreseen CTI and roof line ablation performed with other catheters outside PVI;
- Analysis of different anaesthesia techniques (General anaesthesia with or without intubation versus sedation);
- Freedom from AF recurrence in subjects with anatomical variants of PV such as, but not limited to, common ostia, additional pulmonary vein or early branching;
- Freedom from primary effectiveness failure evaluated in subgroups of subjects (termination of AAD versus continuation of AAD after blanking period);
- For subjects undergoing 3D mapping with the Boston Scientific Rhythmia Mapping System and performing a post-procedural map, map information will be collected to determine lesion locations;
- The percentage of subjects that undergo repeat ablation during the course of the clinical follow-up;
- More than one repeat procedure during the blanking period (within 90 days post-index procedure):
- Changes in the quality of life measures (AFEQT and EQ-5D-5L) between baseline and 12 months follow up.
- The percentage of subjects experiencing device-related adverse events;
- Propensity adjusted comparison of procedural and therapy success between POLAR ICE (NCT04250714) and POLAR SMART.

* LA dwell time is defined as time from the Cryoablation Catheter introduced in the LA to the last time of Cryoablation Catheter exiting the LA.

11.3.6. Changes to Planned Analyses

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

12. Data Management

12.1. *Data Collection, Processing, and Review*

Subject data will be recorded in a limited access secure EDC system, recommended within 10 business days.

The clinical database will reside on a production server hosted by Medidata EDC System. All changes made to the clinical data will be captured in an electronic audit trail and available for review by the sponsor or its representative. The associated Rave software and database have

been designed to meet regulatory compliance for deployment as part of a validated system compliant with laws and regulations applicable to the conduct of clinical studies pertaining to the use of electronic records and signatures. Database backups are performed regularly.

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

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

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 of the closeout activities are completed a request to IT is submitted to have the "Database Locked" or Decommissioned and all database access revoked.

The data reported on the eCRFs shall be derived from source documents and shall be consistent with these source documents. Any discrepancies shall be explained in writing. Any change or correction made to the clinical data will be dated, initialed, and explained, if necessary, and shall not obscure the original entry. A written audit trail shall be maintained which will be made available for review by BSC or its representative. Refer to the eCRF Completion Guidelines when completing the eCRF.

12.2. *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.

12.3. *Technical Source Forms*

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

Collection and completion of all information on the Technical Source Form is the responsibility of the appropriately delegated site personnel.

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

- the Delegated Site Personnel completing the form;
- the Delegated Investigator conducting and/or supervising the case.

12.4. *Quality of Life (QOL)*

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

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 dimension.

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

13. 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 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 study. 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 EDC. Sites may also be required to report deviations to the IRB/EC, per local guidelines and government regulations.

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

The sponsor will not approve protocol waivers.

14. Compliance

14.1. *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 ISO 14155: Clinical Investigation of Medical Devices for Human Subjects - Good Clinical Practice, relevant parts of the ICH Guidelines for GCP, 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 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 or regulatory authority shall be followed, if appropriate.

14.2. *Investigator Responsibilities*

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

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

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

14.2.1. Delegation of Responsibility

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

14.3. *Institutional Review Board/ Ethics Committee*

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

A copy of the written IRB/EC 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. 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 before the changes are implemented to the study. All changes to the ICF will be IRB/EC 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 approval and renewals will be obtained throughout the duration of the study as required by applicable local/country laws or regulations or IRB/EC requirements. Copies of the study reports and the IRB/EC continuance of approval must be provided to the sponsor.

14.4. *Sponsor Responsibilities*

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

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

14.4.1. 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 cryoablation procedure, testing required by the protocol, and follow-ups. Support may include HCP training, addressing HCP questions, or providing clarifications to HCPs concerning the operation of BSC equipment/devices.

At the request of the investigator and while under investigator supervision as allowed by local regulations, BSC personnel may operate equipment during cryoablation 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 Console 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 (Console and applicable accessories) and interpretation of information contained therein to support the collection of required information by the delegated site staff;
- Print out reports/export data directly from the console and provide original printouts or electronic data reports 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.

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 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
- Independently collect critical study data (defined as primary or secondary endpoint data)
- Enter data in electronic data capture systems or on paper case report forms
- Participate in Subject Consent process

14.5. *Insurance*

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

15. 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 sponsor will put a plan in place to document the specific monitoring requirements.

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

16. Potential Risks and Benefits

16.1. *Instructions for Use (IFU)/ Tenpubunsyo*

Refer to the IFU/ Tenpubunsyo for an overview of anticipated adverse (device) effects, and risks associated to the commercial device(s).

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

There are no specific tests outside SOC for PVI Cryo catheter ablation of AF required by this clinical study protocol. Therefore, there is no foreseen increased risk to subjects for participating in the study.

In addition to SOC, the protocol requires the completion of quality of life questionnaires.

16.3. *Risk Minimization Actions*

Additional risks may exist. Risks can be minimized through compliance with this protocol, using the devices in accordance with their applicable IFU/Tenpubunsyo performing procedures in the appropriate hospital environment, following recommended standard practices/guidelines, adherence to subject selection criteria, close monitoring of the subject's physiologic status during procedures and/or follow-ups and by promptly supplying BSC with all pertinent information required by this protocol.

16.4. *Anticipated Benefits*

Subjects may not receive any direct benefit from participating in this study as compared to the current SOC received for treatment of AF.

The collected data will help to collect safety and performance data for Japan and South Korea specifically and collect information on the efficacy of the Cryoablation System if used in today's SOC. The data will help indirectly to improve and optimize current practice.

16.5. *Risk to Benefit Rationale, if applicable*

Risk management activities, including Hazard Analyses (HA) and Failure Mode Effects Analyses (FMEA), have been performed on the Cryoablation System, steerable sheath and extension cable 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.

17. Safety Reporting

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

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

- All Serious Adverse Events, including all events leading to death;
- All Thromboembolic Events;
- All Study Procedure Related AEs (index and repeat procedure);
- All Study Device-Related Adverse Events;
- All Study Related Device Deficiencies;
- Unanticipated Adverse Device Effects/Unanticipated Serious Adverse Device Effects previously not defined in the IFU;
- All BSC Commercialized Device-Related Adverse Events;

When possible, the medical diagnosis should be reported as the Event Term instead of individual symptoms.

If it is unclear whether or not an event fits one of the above categories, or if the event cannot be isolated from the device or procedure, it should be submitted as an adverse event and/or device deficiency.

Any reportable event, experienced by the study subject after informed consent, whether prior to, during or subsequent to the procedure, must be recorded in the eCRF.

Underlying diseases and chronic conditions are not reported as AEs unless there is an increase in severity or frequency during the course of the investigation. Death should not be recorded

as an AE, but should only be reflected as an outcome of one (1) specific SAE (see Table 17.2-1 for AE definitions).

Death should not be recorded as an SAE but should only be reflected as an outcome of one (1) specific SAE (see Table 17.2-1 for Safety definitions).

If the subject experiences a new arrhythmia between index procedure and end of study, and the investigator considers this adverse event to be procedure related, it needs to be reported.

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

- Pre-existing diseases or conditions (including AF, 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;
- A recurrence of an arrhytmia should be reported on the "AF recurrence" eCRF and should not be recorded as an adverse event, unless it meets seriousness criteria as per table 17.2-1;
- Pre-planned hospitalizations at time of enrollment or for a pre-existing condition;
- If an additional ablation procedure is required, this additional ablation procedure should not be considered as an Adverse Event, unless associated with subject worsening condition or a new diagnosis. If the investigator considers this event to be related to any procedure, the event needs to be reported. In this case, the additional ablation procedure should be reported in the Adverse Event eCRF as corrective action of the specific Procedure Related Adverse Event reported for the worsening condition or new diagnosis.

Refer to IFU/ Tenpubunsyo for the known risks associated with the commercial device(s).

17.2. *Definitions and Classification*

Adverse event definitions are provided in Table 17.2-1. Administrative edits were made on the safety definitions from applicable regulations and guidance including (but not limited to) 21 CFR Part 812, ISO 14155 and EU MDR 2017/745/MDCG 2020-10/1 Guidance on Safety Reporting in Clinical Investigations for clarification purposes.

Table 17.2-1: Safety Definitions

Term	Definition
Adverse Event (AE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the study medical device and whether anticipated or unanticipated. **NOTE 1**: This includes events related to the study 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 study medical device.

Table 17.2-1: Safety Definitions

Term	Definition
Adverse Device Effect (ADE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	Adverse event related to the use of the study medical device **NOTE 1**: This includes any adverse event resulting from insufficiencies or inadequacies in the IFU/Tenpubunsyo, the deployment, the implantation, the installation, the operation, or any malfunction of the study medical device. **NOTE 2**: This definition includes any event resulting from use error or from intentional misuse of the study medical device. **NOTE 3**: This includes 'comparator' if the comparator is a medical device.
Serious Adverse Event (SAE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	Adverse event that led to any of the following: a) death, b) serious deterioration in the health of the subject, users or other persons as defined by either: 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, including chronic diseases, or 3) in-patient hospitalization or prolongation of existing hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function c) foetal distress, foetal 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: MDCG 2020-10/1*	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated Adverse Device Effect (UADE) *Ref: 21 CFR Part 812*	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.
Unanticipated Serious Adverse Device Effect (USADE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	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 assessment.

Table 17.2-1: Safety Definitions

Term	Definition
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: MDCG 2020-10/1*	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.
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. Note: new adverse events occurring during the hospitalization are evaluated to determine if they prolonged hospitalization or meet another SAE criteria.

17.3. *Relationship to Study Device(s)*

The investigator must assess the relationship of the reportable AE to the study device, and/or study procedure. See criteria in Table 17.3-1.

Table 17.3-1: Criteria for Assessing Relationship of Study Device(s) or Procedure to Adverse Event

Classification	Description
Not Related *Ref: MDCG 2020-10/1*	Relationship to the device, comparator or procedures can be excluded when: - the event has no temporal relationship with the use of the study device or the procedures related to the use of the study device; - 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 that cannot be affected by the device or procedure; - the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors); - the event does not depend on a false result given by the study device used for diagnosis, when applicable; - 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: MDCG 2020-10/1*	The relationship with the use of the study 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 where relatedness cannot be assessed or no information has been obtained should also be classified as possible.
Probably Related *Ref: MDCG 2020-10/1*	The relationship with the use of the study device or, comparator, or the relationship with procedures seems relevant and/or the event cannot be reasonably explained by another cause.
Causal Relationship *Ref: MDCG 2020-10/1*	The serious event is associated with the study device, comparator or with procedures beyond reasonable doubt when: - the event is a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has a temporal relationship with the study device use/application or procedures; - the event involves a body-site or organ that -the study device or procedures are applied to; -the study device or procedures have an effect on; - the serious event follows a known response pattern to the medical device (if the response pattern is previously known); - the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible); - other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;

	- harm to the subject is due to error in use; - the event depends on a false result given by the study device used for diagnosis, when applicable; - In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

17.4. *Investigator Reporting Requirements*

The communication requirements for reporting to BSC are as shown in Table 17.4-1: Investigator Reporting Requirements

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

POLARSMART.Safety@BSCI.COM

Table 17.4-1: Investigator Reporting Requirements

Event Classification	**Communication Method**	**Communication Timeline post-market studies*** (*EU MDR 2017/745, MDCG 2020-10/1*MEDDEV 2.12/1: GUIDELINES ON A MEDICAL DEVICE VIGILANCE SYSTEM)
Unanticipated Adverse Device Effect / Unanticipated Serious Adverse Device Effect	Complete AE eCRF page with all available new and updated information.	• Within 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.	• Upon request of sponsor.
Serious Adverse Event	Complete AE eCRF page with all available new and updated information.	• Within 10 calendar days after becoming aware of the event or as per local/regional regulations. • All death events must be reported within 3 calendar days • Reporting required through the end of the study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• When documentation is available • Upon 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.

Event Classification	Communication Method	Communication Timeline post-market studies* (*EU MDR 2017/745, MDCG 2020-10/1*MEDDEV 2.12/1: GUIDELINES ON A MEDICAL DEVICE VIGILANCE SYSTEM)
		• Reporting required through the end of the study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• When documentation is available • Upon request of sponsor
Device Deficiencies (including but not limited to malfunctions, use errors, and inadequacy in information supplied by the manufacturer, including labelling) Note: Any Device Deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, circumstances had been less fortunate is considered a reportable event.	Complete DD eCRF 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.	• Upon 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.	• Adverse Device Effects (or other key events of interest, e.g., Heart Failure): In a timely manner but not later than 30 business days after becoming aware of the information • Adverse Events: In a timely manner but recommend within 30 business days after becoming aware of the information • Reporting required through the end of study • Upon request of sponsor
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	

17.5. *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 will be documented and reported to BSC (as per table 17.4-1). If possible, the device(s) should be returned to BSC for analysis. Instructions for returning the device(s) will be provided upon request. If it is not possible to return the device, the investigator should document why the device was not returned and the final disposition of the device. Device deficiencies should also be documented in the subject's source records.

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

17.6. *Reporting to Regulatory Authorities / IRBs / ECs / Investigators*

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

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

17.7. *Subject Death Reporting*

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

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

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

Also submit the following documentation, upon request from sponsor:

If the subject expired in the hospital:

- A copy of the medical records for that admission (e.g., H&P, consults, test results, operative reports, and/or progress notes from the hospital chart);
- Death certificate (if available);
- Autopsy report (if applicable);
- If applicable, the Boston Scientific catheters should be returned promptly to Boston Scientific CRM/EP for analysis.

If the subject expired outside of the hospital (e.g., home):

- A copy of the most recent clinic visit (if not already submitted to Boston Scientific);
- Death certificate (if available).

18. 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 study devices, study-required procedures and/or testing, or data collection.

The obtaining and documentation of Informed Consent must be in accordance with the principles of the Declaration of Helsinki, ISO 14155, any applicable national regulations, and local Ethics Committee and/or Regulatory authority, as applicable. The ICF must be accepted by BSC or its delegate (e.g. CRO), and approved by the site's IRB/EC, 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. 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 approval prior to their use. Privacy language shall be included in the body of the form or as a separate form as applicable.

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

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

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

Failure to obtain subject consent will be reported by BSC to the applicable regulatory authority according to their requirements (e.g., the principles of the Declaration of Helsinki, local applicable regulation 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), 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. The new version of the ICF must be approved by the IRB/EC. Acceptance by Boston Scientific is required if changes to the revised ICF are requested by the site's IRB/EC. The IRB/EC will determine the subject population to be re-consented.

19. Committees

19.1. *Safety Monitoring Process*

The BSC personnel from the Medical Safety and Safety Trial Operation group 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 documents and other data information. The BSC Medical Safety and Safety Trial Operations team include 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.

19.2. *Steering Committee*

A Steering Committee composed of the sponsor's Clinical Management and the study Coordinating Principal Investigator(s) have been convened. Responsibilities may include oversight of the overall conduct of the study with regard to protocol development, study progress, subject safety, overall data quality and integrity, and first line review and final decision making of independent medical reviewer recommendations, as well as disseminating any study results through appropriate scientific sessions and publications. Steering Committee members may participate in the review and approval of all requests for data analysis, abstract and manuscript preparation, and submission. As appropriate, the Steering Committee may be invited to participate as POLAR SMART Investigators.

19.3. *Other Committee*

Other committee may be added at the discretion of sponsor, the scope and the procedures to be followed will be defined in a separate document.

20. Suspension or Termination

20.1 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, and regulatory authorities, as applicable, will be notified in writing in the event of study termination.

20.1.1 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 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/marketing of the device.

20.2 Termination of Study Participation by the Investigator or Withdrawal of IRB/ EC Approval

Any investigator, or associated IRB/EC 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, and regulatory authorities, as applicable, will be notified in writing in the event of these occurrences.

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

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

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

20.4 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 6 months after site initiation, or if the site has multiple or severe protocol violations/noncompliance without justification and/or fails to follow remedial actions.

In the event of termination of site participation, all devices and testing equipment (Sponsor 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 and regulatory authorities, as applicable, will be notified. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

21. Study Registration and Results

21.1. *Study Registration*

To comply with applicable laws and regulations, the study will be registered on a publicly accessible database.

21.2. *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 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.

21.3. *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. BSC may 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/).

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23. Abbreviations and Definitions

23.1. *Abbreviations*

Abbreviations are shown in Table 23.1-1Table 23.1-1.

Table 23.1-1: Abbreviations

Abbreviation/Acronym	Term
AAD	Anti-Arrhythmic Drugs
ACT	Activated Clotting Time
ADE	Adverse Device Effect

Table 23.1-1: Abbreviations

Abbreviation/Acronym	Term
AE	Adverse Event
AF	Atrial Fibrillation
AF-CB4	Fourth Generation of Arctic Front Cryoballoon
AFEQT	Atrial Fibrillation Effect on Quality of Life Survey
AFL	Atrial Flutter
AT	Atrial Tachycardia
CABG	Coronary artery bypass grafting
CRT	Cardiac Resynchronization Therapy
CS	Coronary Sinus
CTI	Cavotricuspid Isthmus
CVA	Cerebrovascular Accident
DD	Device Deficiency
DMS	Diaphragm Movement Sensor
DVT	Deep Vein Thrombosis
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EP	Electrophysiology
ESC	European Society of Cardiology
HCP	Health Care Personnel
ICB	Inter Connection Box
ICE	Intracardiac Echo
ICF	Informed Consent Form
IFU	Instructions for Use
JCS	Japan Circulation Society
JHRS	Japan Heart Rhythm Society
LA	Left Atrium
LAAO	Left Atrial Appendage Occulsion
MI	Myocardial Infarction
MRI	Magnetic Resonance Imaging
N_2O	Nitrogen Dioxides
PCI	Percutaneous Coronary Intervention
PM	Pacemaker
PMCF	Post Market Clinical Follow-up
PTCA	Percutaneous transluminal coronary angioplasty
PV	Pulmonary Vein
PVI	Pulmonary Vein Isolation
RA	Right Atrium
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
TEE	Trans-esophageal echocardiography
TIA	Transient Ischemic Attack
TSF	Technical Source Form

Table 23.1-1: Abbreviations

Abbreviation/Acronym	Term
TTE	Trans-Thoracic echocardiography
TTI	Time-to-isolation
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect

23.2. *Definitions*

Terms are defined in Table 23.2-1: Definition.

Table 23.2-1: Definition

Term	Definition
Activated Coagulation/Clotting Time	ACT is a test that is used to monitor the effectiveness of high dose heparin therapy.
Arterial-Venous Fistula	Abnormal communication between an artery and a vein.
Atrioesophageal Fistula	A connection between the atrium and the lumen of the esophagus.
Attempt Subject	Any subject that signs the consent form, and has any study device inserted into the body but does not receive any Cryoablation application.
AV block	A conduction disturbance that results in the partial inability of an electrical impulse generated in the atria to reach the ventricles.
Blanking Period	90-day period between ablation procedure and the initiation of the Effectiveness Evaluation Period during which up to one additional ablation procedure 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 has given written informed consent 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 90 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

Table 23.2-1: Definition	
Term	**Definition**
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
Occlusion Grade	Score 4 = excellent (full retention of contrast medium without visible outflow) Score 3 = moderate (incomplete occlusion with slight leakage of contrast medium) Score 2= poor (presence of sustained and massive leakage of contrast medium) Score 1 = very poor (immediate rapid outflow from the PV).
Paroxysmal Atrial Fibrillation	Recurrent symptomatic Atrial Fibrillation that terminates spontaneously or with intervention within seven days of onset.
Pericardial Effusion	A collection of fluid or blood in the pericardial space around the heart or in pleural space around the lungs.
Pericarditis	Inflammation of the pericardium surrounding the heart. Pericarditis should be considered a major complication following ablation if it results in an effusion that leads to hemodynamic compromise or requires pericardiocentesis, prolongs hospitalization by more than 48 hours, requires hospitalization, or persists for more than 30 days following the ablation procedure.
Pneumothorax	Collapse of the lung due to an abrupt change in the intrapleural pressure within the chest cavity.
Primary Effectiveness Failure	A TREATMENT subject with • Acute procedure failure • 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 Days 91 and 12-month post index procedure • Any of the following interventions for atrial fibrillation, or new onset of atrial flutter or atrial tachycardia between Days 91 and 12-month post index procedure: o Repeat AF procedure o Electrical and/or pharmacological cardioversion for AF/AFL/AT o Prescribed a higher dose of any AAD documented at baseline or a new AAD not documented at baseline
Procedural Success	Pulmonary vein isolation achieved with the Boston Scientific cryoablation system as demonstrated by entrance block at the minimum.
Prolonged Hospitalization	Hospitalization ≥72 hours after the study procedure for reasons other than anticoagulation
Pseudoaneurysm	A dilation of an artery with disruption of one or more layers of its walls.

Table 23.2-1: Definition	
Term	**Definition**
Pulmonary Edema/Heart Failure	Ineffective pumping of the heart leading to an accumulation of fluid in the lungs. Typical symptoms include shortness of breath with exertion, difficulty breathing when lying flat and leg or ankle swelling.
Pulmonary Vein Stenosis (Significant)	Pulmonary vein stenosis is defined as a reduction of the diameter of a PV or PV branch. For the primary safety endpoint of this study, significant pulmonary vein stenosis is defined as symptomatic and requiring intervention.
Source Data *Ref: ISO 14155*	All information in original records, certified copies of original records of clinical findings, observations, or other activities in a clinical investigation, necessary for the reconstruction and evaluation of the clinical investigation. This includes source data initially recorded in an electronic format.
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)	Rapid onset of a focal or global neurological deficit with at least one of the following: change in level of consciousness, hemiplegia, hemiparesis, numbness or sensory loss affecting one side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke. Duration of a focal or global neurological deficit ≥24 hours; OR <24 hours if therapeutic intervention(s) were performed (e.g., thrombolytic therapy or intracranial angioplasty); OR available neuroimaging documents a new hemorrhage or infarct; OR the neurological deficit results in death. No other readily identifiable non-stroke cause for the clinical presentation (e.g., brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences). Confirmation of the diagnosis by at least one of the following: neurology or neurosurgical specialist; neuroimaging procedure (MRI or CT scan or cerebral angiography); lumbar puncture (i.e., spinal fluid analysis diagnostic of intracranial hemorrhage).
Symptomatic AF	Required symptom(s) of AF that were experienced by the subject, made them seek medical attention, and were concurrent with a documented episode by ECG, event monitoring and/or Holter monitor. Symptoms may have included palpitations, irregular pulse (i.e. rapid, racing, pounding, fluttering, bradycardic), dizziness, weakness, chest discomfort, and breathlessness.
Thrombus	An aggregation of blood factors, primarily platelets and fibrin with entrapment of cellular elements, frequently causing vascular obstruction at the point of its formation.
Thromboembolism	The blockage of a blood vessel lumen by air or solid material such as device fragments, blood clot or other tissues that have migrated from another anatomic site.
Transient Ischemic Attack (TIA)	New focal neurological deficit with rapid symptom resolution (usually 1 to 2 hours), always within 24 hours; neuroimaging without tissue injury

Table 23.2-1: Definition	
Term	**Definition**
Treatment Subject	Any subject that signs the consent form, and has the specified study devices inserted into the body and undergoes protocol specific treatment (cryoablation) for the intended disease.
Vagal Nerve Injury/Gastroparesis	Vagal nerve injury is defined as injury to the vagal nerve that results in esophageal dysmotility or gastroparesis. Vagal nerve injury is considered to be a major complication if it prolongs hospitalization, requires hospitalization, or results in ongoing symptoms for more than 30 days following an ablation procedure
Vascular access complications	Development of a hematoma, an AV fistula, or a pseudoaneurysm. A major vascular complication is defined as one that requires intervention, such as surgical repair or transfusion, prolongs the hospital stay, or requires hospital admission.

24. Appendices

24.1. *Quality of Life Instruments*

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

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

The Atrial Fibrillation Effect on Quality of Life Survey (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.