Comparison of Anticoagulation with Left Atrial Appendage Closure after AF Ablation

OPTION

CLINICAL INVESTIGATION PLAN

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Revision Version	Protocol Date	Template number and version	Protocol Section Modified	Summary of Changes	Justification for Modification
A	14DEC2018	Template 90702637_Rev/Ver AJ	NA	NA	NA
B	09APR2019	Template 90702637_Rev/Ver AL	Section 5	Updated Indications for Use	To clarify current device indication for countries where CE mark applies
			Section 8	Updated Roll-in subject information	To clarify which sites, require Roll-ins, as well as the expected number of Roll-ins
			Section 9	Updated Inclusion criteria	To clarify determination of suitability for the defined protocol pharmacologic regimen
			Section 11	Updated data collection requirements	To clarify what is required to be collected at each visit
			Section 11	Added blinding for Quality-of-Life Questionnaires and stroke scales	Based on FDA feedback
			Section 11	Added language around what should be done if a subject's NIHSS and/or MRS have changed and/or if there is suspicion of a neurologic event	Based on FDA feedback
			Section 11	Added language around incomplete device seal and follow-up imaging	Based on FDA feedback

Revision Version	Protocol Date	Template number and version	Protocol Section Modified	Summary of Changes	Justification for Modification
			Section 13	Updated statistical language	To correct errors, as well as clarify study analyses
			Section 17	Updated language around the OPTION DFU	To clarify relationship between the OPTION DFU and the commercial DFU for countries where the CE mark applies
C	15Jan2020	Template 90702637_Rev/Ver AL	Section 4	Updated clinical study overview	To accurately reflect study statuses
			Section 8	Added language regarding implant of roll-in subjects as opposed to enrollment of roll-in subjects	To better align with the purpose of gaining implant experience via roll-in subjects prior to enrollment in the randomized cohort
			Section 8	Increased the global number of sites to 150	To increase the study enrollment rate
			Section 9	Additional language regarding the use of other cardiac imaging modalities to determine exclusion. Correction of Exclusion Criteria #4 to add "…and cardioversion"	To allow for standard of care assessments to be used for determining subject eligibility. EC #4 corrected in section 9.3 to match existing protocol synopsis from Rev B.
			Section 11	Added a section regarding Roll-In subject windows	To clarify visit timing for Roll-In subjects
			Section 11	Included "High-risk PFO not detected at baseline" as a reason to not proceed with implant.	To align with TTE exclusion criteria

Revision Version	Protocol Date	Template number and version	Protocol Section Modified	Summary of Changes	Justification for Modification
			Section 11	Added detail for randomization design defined as 1:1 (device: control)	To provide clarity of design
			Section 12	Added the following note: Clinical study data establishing safety and effectiveness are based on demonstration of peri-device flow ≤5 mm as a measure of adequacy of LAA seal. Per the WATCHMAN FLX DFU, if adequate seal is not demonstrated, decision to discontinue OAC is at physician discretion provided that any leak demonstrated is ≤ 5 mm. Non-approved measures/procedures to improve seal (e.g. 'kissing' WATCHMAN, vascular plugs, endovascular coils, etc.) must not be attempted during the course of this study.	Reattempts at closure for any leak size has not been proven in randomized clinical trials to be safe and/or effective.
			Section 13	Added the failure to discontinue AAD after the blanking period as failure	To be consistent with medical literature.
D	25Sep2020	Template 90702637_Rev/Ver AM	Section 4	Updated clinical study overview	To accurately reflect study statuses
			Section 4	Added note that next generation WATCHMAN Access Systems may become available during enrollment and they may be considered for the trial.	To avoid a future protocol amendment due to commercialization of next generation WATCHMAN Access Systems.

Revision Version	Protocol Date	Template number and version	Protocol Section Modified	Summary of Changes	Justification for Modification
			Section 8	Updated medication discontinuation requirements to align with study visits	To avoid deviations if a medication is stopped within a visit window
			Section 11	Added additional language allowing ICE at implant and CT for follow-up imaging	Based on Steering Committee feedback to reduce intubations during the COVID pandemic.
			Section 11	Updated timing on baseline TTE from 60 days prior to randomization to 180 days prior to randomization	Based on Steering Committee feedback, to provide sites more flexibility, and reduce the likelihood of unnecessary additional procedures.
			Section 11	Updated data collection requirements and schedule	To add new imaging modalities, and allow recent hemoglobin and platelet values within a subject's medical record to be used at baseline
			Section 11	Updated AF assessment type to include long standing persistent	To make clear that all AF types are being recorded in the study
			Section 20	Updated table of Anticipated Adverse Events	To align with IFU
			Section 21	Updated AE recurrence reporting requirements	To better clarify when an event meets reporting criteria
			Section 21	Updated Safety Definitions table, Relationship table, and Investigator Reporting Requirements table	To incorporate new regulations and provide further clarity

Revision Version	Protocol Date	Template number and version	Protocol Section Modified	Summary of Changes	Justification for Modification
E	14Jan2022	Template 90702637_Rev/Ver AP	Section 4	Updated WATCHMAN Clinical Studies Status	To provide further information as to which studies have been completed.
			Section 10	Updated the Device Group Classification	To provide further instructions to sites about subject classification status
			Section 10	Updated "lost to follow up" definition	To provide further clarity to the number of attempts in which to contact patients that are lost to follow up.
			Section 11	Updated Data Collection Schedule	To provide further details for the follow up visits that are conducted by phone or office.
			Section 11	Updated Follow procedures	To provide the option for office or phone call visits and associated study procedures to be done given the current environment with COVID-19. Additionally, to provide guidance if outside facility standard of care assessment data usage.
			Section 11	Local Laboratory	To clarify lab certification documentation filing requirements.
			Section 12	Updated Crossover Group	To clarify CRF information to entered in EDC for patients that had crossed over.

Revision Version	Protocol Date	Template number and version	Protocol Section Modified	Summary of Changes	Justification for Modification
			Section 21	**Updated Safety Reporting Section**	**To further clarify event reporting requirements and updated due to regulations referenced**
			Section 28	**Updated References**	**To provide additional references to the updates in status for WATCHMAN Clinical trials.**
			Section 29	**Updated Definitions**	**To provide further detail to the definitions**

2. Protocol Synopsis

Comparison of Anticoagulation with Left Atrial Appendage Closure after AF Ablation (**OPTION**)	
Study Objective(s)	The primary objective of this study is to determine if left atrial appendage closure with the WATCHMAN FLX Device is a reasonable alternative to oral anticoagulation following percutaneous catheter ablation for high risk patients with non-valvular atrial fibrillation.
Planned Indication(s) for Use	The planned indication for use within the OPTION study is as follows: The WATCHMAN and WATCHMAN FLX Device are indicated to reduce the risk of thromboembolism from the left atrial appendage in subjects with non-valvular atrial fibrillation who: • Are at increased risk for stroke and systemic embolism based on CHA_2DS_2-VASc scores following catheter ablation of atrial fibrillation; and • Are deemed to be suitable for anticoagulation therapy Note: In countries where CE mark applies, the OPTION indication is within the CE mark approved Indication for Use.
Study Design	This study is a prospective, randomized, multi-center, global investigation to determine if left atrial appendage closure with the WATCHMAN FLX Device is a reasonable alternative to oral anticoagulation in patients after AF ablation.
Planned Number of Subjects	A maximum of 1600 subjects will be randomized in the study. *Note the total number of enrolled patients is expected to exceed the number of randomized subjects since sites without WATCHMAN FLX experience are required to perform two roll-in cases. A maximum of 260 patients will be treated in the roll-in phase of the study, including approximately 130 roll-in subjects in the United States.* *The roll-in cohort will be analyzed separately from the primary cohort of randomized subjects.*
Planned Number of Centers / Countries	Up to 150 investigational centers worldwide

Comparison of Anticoagulation with Left Atrial Appendage Closure after AF Ablation (**OPTION**)	
Primary Effectiveness Endpoint	WATCHMAN therapy is non-inferior for the occurrence of stroke (including ischemic and/or hemorrhagic), all cause death, and systemic embolism at 36 months.
Primary Safety Endpoint	WATCHMAN therapy is superior for non-procedural bleeding through 36 months (ISTH major bleeding and clinically relevant non-major bleeding)
Secondary Endpoint	WATCHMAN therapy is non-inferior for ISTH major bleeding at 36 months (including procedural bleeding)
Additional Analysis	The occurrence of: • Stroke • Ischemic stroke • Hemorrhagic stroke • Disabling stroke • Non-disabling stroke • Systemic embolism • Procedural and non-procedural bleeding • All-cause death • Cardiovascular/unknown death • Non-cardiovascular death • Device related Thrombus • Device Seal • Single procedure freedom from AF • Healthcare resource utilization • Quality of life
Method of Assigning Patients to Treatment	A subject who signs informed consent is considered enrolled in the study. Subjects will be randomized to OAC or WATCHMAN FLX in equal fashion. Randomization will be stratified by sequential vs. concomitant planned ablation to help ensure balance of treatment assignments within the sequential and concomitant groups.
Follow-Up Schedule	Study procedures and follow-up visits will occur as follows: • Consent – Must be obtained within 30 days prior to randomization • Randomization ○ Prior ablation (Sequential group) – randomization must be performed between 90 and 180 days after the most recent AF ablation procedure. WATCHMAN FLX Implant – must be

Comparison of Anticoagulation with Left Atrial Appendage Closure after AF Ablation (**OPTION**)	
	performed within 10 days following randomization if subject is randomized to the device arm ○ Planned prospective ablation (Concomitant group) – the ablation +/–WATCHMAN FLX Implant must be performed within 10 days of randomization • 3 Month Follow-up (90 ± 15 days from randomization) • 12-Month Follow-up (365 ± 30 days from randomization) • 24-Month Follow-up (730 ± 60 days from randomization) • 36-Month Follow-up (1095 + 60 days from randomization) – this follow-up must occur on or after 1095 days and on or before 1155 days Note: for Roll-in subjects the date of implant will be used to calculate Follow-up windows instead of the date of randomization.
Study Duration	The duration of the study is expected to last approximately 64 months. The duration of individual subject participation is expected to last approximately 36 months but may vary per subject.
Control Group Medication Therapy	Following randomization, control subjects must continue or start market-approved OAC used per IFU for atrial fibrillation stroke prevention and should remain on it for the duration of the trial.
Device Group Medication Therapy	After the WATCHMAN FLX implant, Device Group subjects will be prescribed market-approved OAC and aspirin (75-100mg recommended) until the 3-month visit followed by aspirin until at least the 12-month visit (recommended for duration of the trial).
Test Device and sizes	The WATCHMAN FLX Left Atrial Appendage Closure Device with Delivery System (consisting of the Delivery Catheter with a pre-loaded Closure Device) WATCHMAN FLX is available in 20, 24, 27, 31, and 35mm models to fit left atrial appendage ostia widths ranging from 14.0 - 31.5mm.
Inclusion Criteria	1. The subject is of legal age to participate in the study per the laws of their respective geography. 2. Underwent a prior catheter ablation procedure for non-valvular AF between 90 and 180 days prior to randomization (sequential) or is planning to have clinically indicated catheter ablation within 10 days of randomization (concomitant). 3. The subject has a calculated CHA2DS2-VASc score of 2 or greater for males or 3 or greater for females.

Comparison of Anticoagulation with Left Atrial Appendage Closure after AF Ablation (**OPTION**)	
	4. The subject is deemed by the treating physician to be suitable for the protocol defined pharmacologic regimens. 5. The subject is able to undergo TEE examinations. 6. The subject or legal representative is able to understand and is willing to provide written informed consent to participate in the trial. 7. The subject is able and willing to return for required follow-up visits and examinations.
Exclusion Criteria	1. The subject is currently enrolled in another investigational study that would directly interfere with the current study, except when the subject is participating in a mandatory governmental registry, or a purely observational registry with no associated treatments. Each instance must be brought to the attention of the sponsor to determine eligibility, regardless of type of co-enrollment being proposed. 2. The subject requires long-term anticoagulation therapy for reasons other than AF-related stroke risk reduction, for example due to an underlying hypercoagulable state (i.e., even if the device is implanted, the subjects would not be eligible to discontinue OAC due to other medical conditions requiring chronic OAC therapy). 3. The subject is deemed by the treating physician to be unsuitable for chronic anticoagulation and/or aspirin therapy due to bleeding risk, allergy, or other reasons. 4. The subject had or is planning to have any cardiac or major non-cardiac interventional or surgical procedure (excluding non-valvular AF ablation and cardioversion) within 30 days prior to or 60 days after randomization [including, but not limited to: percutaneous coronary intervention (PCI), other cardiac ablation (VT ablation, etc.), etc.]. 5. The subject had a stroke or transient ischemic attack (TIA) within the 60 days prior to randomization. 6. The subject had a prior major bleeding event per ISTH definition within the 14 days prior to randomization. Lack of resolution of related clinical sequelae, or planned and pending interventions to resolve bleeding/bleeding source, are a further exclusion regardless of timing of the bleeding event. 7. The subject has had a myocardial infarction (MI) documented in the clinical record as either a non-ST elevation MI (NSTEMI) or as an ST-elevation MI (STEMI), with or without intervention, within 90 days prior to randomization. 8. The subject has a history of atrial septal repair or has an ASD/PFO device.

Comparison of Anticoagulation with Left Atrial Appendage Closure after AF Ablation (**OPTION**)	
	9. The subject has an implanted mechanical valve prosthesis in any position. 10. The subject is of childbearing potential and is, or plans to become pregnant during the time of the study (method of assessment upon study physician's discretion) 11. The subject has a documented life expectancy of less than two years. 12. The subject has a cardiac tumor. 13. The subject has signs/symptoms of acute or chronic pericarditis. 14. There is evidence of tamponade physiology. 15. The subject has contraindications (anatomical or medical) to percutaneous catheterization procedures. 16. The subject has documented NYHA Class IV heart failure. 17. The subject has documented surgical closure of the left atrial appendage. 18. The subject has an active infection.
Transthoracic Echo Exclusion Criteria	1. The subject has LVEF < 30% 2. The subject has an existing pericardial effusion with a circumferential echo-free space > 5mm. 3. The subject has a high- risk patent foramen ovale (PFO) with an atrial septal aneurysm excursion > 15mm or length > 15mm. 4. The subject has a high-risk PFO with a large shunt defined as early, within 3 beats and/or substantial passage of bubbles. 5. The subject has significant mitral valve stenosis (i.e., MV area <1.5 cm^2). Note: Criteria obtained from cardiac imaging performed within 180 days prior to randomization may be used if all the exclusion criteria can be evaluated.
Multiple Interventions During Index Procedure	Percutaneous catheter ablation using currently available non-surgical standard techniques and market-approved technology may be performed at the time of the WATCHMAN FLX implant procedure **only for Concomitant Ablation subjects** • The procedures must occur on the same day with the ablation occurring prior to the WATCHMAN FLX implant. • Catheter ablation of the LAA, non-standard ablation techniques (e.g. CFAEs and hybrid ablation) and any non-AF-related ablation (e.g. VT) are not permitted. • Other concomitant procedures are also not permitted, including, but not limited to, transcutaneous valve procedures, pacemaker or ICD generator change, etc.

Note: Sequential Ablation subjects who need a repeat ablation cannot combine it with the WATCHMAN FLX implant procedure.
For all patients, cavotricuspid isthmus (CTI) ablation and cardioversion may be performed during ablation.

Statistical Test Method

Hypotheses testing in this study will use standard statistical methodology. Each primary endpoint will be assessed vs. a performance goal. To declare success, the primary endpoints must be met. The details of each endpoint analysis are listed in the table below.

Endpoint	Assessment period	Expected Rate	Non-Inferiority Margin	Test (α=2.5%) NI (α=5%) Sup	Expected Attrition	Power subjects
Primary Efficacy Endpoint	36-month follow-up visit	10% in both arms	5%	One-sided NI Test of KM event rates	15%	84% (N=1600)
Primary Safety Endpoint	36-month follow-up visit	Device: 14% Control: 20%	NA	Two-sided log-rank test	20%	>86.4% (N=1600)
Secondary Endpoint	36-month follow-up visit	Device: 11% Control: 11%	5.25%	One-sided NI Test of KM event rates	20%	84.3% (N=1600)

3. Table of Contents

3.1. *Table of Figures*

3.2. *Table of Tables*

4. Introduction

4.1. *Background*

Atrial fibrillation (AF) is one of the most common abnormal rhythm disturbances and affects approximately 5.5 million people worldwide, including 10% of people older than 75 [1]years. There are many factors that cause and sustain atrial fibrillation making treatment strategies difficult for clinicians. Symptoms of AF can be minor to severe. The most debilitating consequence of AF is thrombus formation from stagnant blood flow leading to thromboembolism and stroke. As such, the rate of ischemic stroke attributed to non-valvular AF is estimated to average 5% per year, which is 2-7 times that of those without AF[2]. Thus, thromboembolic protection in patients with AF at high risk of stroke is central to treatment.

Treatment with warfarin therapy for the prevention of thromboemboli originating in the left atrial appendage has been well documented [3-5]. Warfarin therapy targeting an International Normalized Ratio (INR) between 2.0 – 3.0 has been considered the gold standard treatment historically for patients with non-valvular AF for prevention of stroke. While warfarin has remained the optimum treatment for many years, there are numerous challenges with the drug, such as frequent need for monitoring and dosage adjustments, dietary and metabolic interactions, and concerns of patient compliance. Additionally, the potential for frequent and fatal bleeding are high concerns for patients and caregivers, and often it is found this drug is not well tolerated [6,7].

Currently available alternatives to warfarin are the direct oral anticoagulants (DOACs), which include dabigatran, rivaroxaban, apixaban, and edoxaban. Unlike warfarin, DOACs can be administered without the need for monitoring, have fewer food and drug interactions, and provide an improved effectiveness/safety ratio. Dabigatran at the dose of 150 mg twice daily is shown to be superior to warfarin in prevention of stroke and systemic thromboembolism, has a favorable safety profile including significantly less intracranial bleeding and comparable extracranial bleeding, and is associated with less cardiovascular mortality [7-10]. Rivaroxaban at a daily dose of 20 mg is shown to be noninferior to warfarin in prevention of stroke or systemic embolism. The risk of major bleeding is not significantly different for rivaroxaban versus warfarin; however, intracranial and fatal bleeding is less frequent with rivaroxaban [11]. In comparison to warfarin, apixaban at a dose of 5 mg twice daily is also shown to be superior in prevention of stroke and systemic thromboembolism, causes less bleeding, and is associated with a lower mortality rate [12]. Edoxaban is shown to be non-inferior to warfarin with respect to the prevention of stroke or systemic embolism, and is associated with significantly lower rates of bleeding and death from cardiovascular causes [13]. While DOACs significantly reduce the need for frequent monitoring, dosage adjustments, and dietary and metabolic interactions, there are still concerns of patient compliance and bleeding complications with these newer agents.

Additionally, patients in AF may seek symptom relief through cardiac ablation treatment in an effort to maintain normal sinus rhythm. While cardiac ablation can be effective at reducing the symptoms associated with the arrhythmia, OAC is still recommended. Both the ACC/AHA/HRS and ESC Guidelines currently recommend continued OAC after an AF

catheter ablation procedure for patients at risk for stroke. The 2017 HRS AF consensus document provides rationale for why anticoagulation should not be stopped post ablation:

1. Recurrences of AF are common both early and late following AF ablation
2. Asymptomatic AF is common, and is more common following AF ablation than prior to AF ablation
3. AF ablation destroys a portion of the atria and the impact of this on stroke risk is uncertain
4. There have been no large, randomized prospective trials that have assessed the safety of discontinuing OAC in post-Ablation patients
5. Studies have shown that strokes in patients with AF might not be related to an AF event

Despite the above, many patients desire to stop OAC after catheter ablation because they are no longer symptomatic.

As the risk of stroke increases with age and the disability and tolerance concerns with available drug therapy persist, the need for permanent protection against thromboembolism in AF patients remains unmet. The sponsor developed the WATCHMAN™ and WATCHMAN FLX™ Left Atrial Appendage Closure (LAAC) Device, a permanent implantable device to seal off the left atrial appendage, the location where the vast majority of thrombi originate in AF patients. This device has been shown to provide an alternative to warfarin therapy in non-valvular AF patients who require thromboembolic protection. The current study is designed to determine if left atrial appendage closure with the WATCHMAN FLX Device is a reasonable alternative to oral anticoagulation, including warfarin and the direct oral anticoagulants, following percutaneous catheter ablation for non-valvular atrial fibrillation.

4.2. *WATCHMAN Therapy*

Two generations of the WATCHMAN Closure Device with Delivery System, as identified in the **Table 4.1**, are discussed below. The WATCHMAN Access System (required accessory for use in WATCHMAN procedures) and each generation of the WATCHMAN Closure Device with Delivery System are provided sterile and as single use devices.

Table 4.1: Description of WATCHMAN Products

Name	Description
WATCHMAN™ Access System	The first CE-marked and FDA-approved generation of the WATCHMAN Access System. This Access System may be used with either the WATCHMAN (Gen 2.5) or WATCHMAN FLX Closure Device with Delivery System
WATCHMAN TruSeal Access System	Boston Scientific's next CE-marked and FDA-approved generation WATCHMAN Access System.

Name	Description
WATCHMAN™ LAA Closure Device with Delivery System	The first commercialized generation of the WATCHMAN LAA Closure Device with Delivery System (note: also referred to internally as Gen 2.5).
WATCHMAN FLX™ Closure Device with Delivery System	Boston Scientific's next generation WATCHMAN LAA Closure Device with Delivery System.

For simplicity, the two generations of the Closure Device with Delivery System will be referenced as WATCHMAN (Gen 2.5) and WATCHMAN FLX and the implanted portion of the products will be referred to as the Closure Device. Additional next generation WATCHMAN Access Systems may become available during enrollment. If they are approved or cleared for commercial use, they may be considered for this trial.

The implanted component of the study device, hereafter referred to as the WATCHMAN FLX Device, is designed to prevent the embolization of thrombi that may form in the LAA. The WATCHMAN FLX Device may reduce the occurrence of ischemic stroke and systemic thromboembolism in patients with non-valvular AF who require treatment for potential thrombus formation. It may also reduce the risk of life-threatening bleeding events such as hemorrhagic stroke by potentially removing the need for anticoagulation therapy.
A first generation of FLX device (FLX 1.0) was evaluated in a limited market release following CE mark. Feedback from that experience was incorporated into the design of the next generation FLX (FLX 2.0) currently employed in this study. The current WATCHMAN FLX device received CE mark in February 2019 and FDA approval in July 2020.

Various clinical trials have established the safety and performance of the WATCHMAN LAA Closure Technology (Access System and Delivery System) which is designed to prevent thrombus embolization from the left atrial appendage and reduce the risk of life-threatening bleeding events in patients with non-valvular atrial fibrillation. **Table 4.2** outlines the various clinical trials. The EVOLVE study tested safety and efficacy in what was at the time the next-generation WATCHMAN (Gen 4) device. The PINNACLE FLX test the safety and efficacy of the WATCHMAN FLX device.

Table 4.2: Clinical Studies of the WATCHMAN™ or WATCHMAN FLX™ Device

Study	Dates of Enrollment	Enrolled Subjects	Sites	Follow-Up
Pilot (feasibility study)	Aug 2002 – Jan 2005	66	8	U.S. subjects completed 5 years; OUS subjects completed up to 9 years.
PROTECT AF (pivotal study)	Feb 2005 – Jun 2008	800	59	Complete through 5 years
CAP Registry	Aug 2008 – Jun 2010	566	26	Complete
ASAP	Jan 2009 – Nov 2011	150	4	Complete

Study	Dates of Enrollment	Enrolled Subjects	Sites	Follow-Up
(feasibility study)				
EVOLVE (registry)	May 2009 – June 2011	69	3	Complete
PREVAIL (pivotal study)	Nov 2010 – Jun 2012	461	41	Complete
CAP2 Registry	Sep 2012 – Mar 2014	579	47	Complete
EWOLUTION (EU registry)	Oct 2013 – May 2015	1020	47	Complete
WASP (Asia Pacific Registry)	Jan 2014 – Oct 2015	201	9	Complete
WATCHMAN NESTed (US PAS)	Mar 2016-Nov 2016	2000	All commercial sites	Follow up ongoing through 5 years
SALUTE (Japan study)	Feb 2017-July 2017	71	10	Complete
ASAP-TOO (OAC contraindicated population)	Feb 2017-Oct 2020	888	Up to 130	Enrollment closed; follow-up ongoing through 5 years
PINNACLE FLX	May 2018- Nov 2018	400	29	Complete
FLXIBILITY	Jul 2019 – Jul 2020	300	17	Ongoing through 1 year
ICE LAA	July 2020-Aug 2021	100	10	Complete
CHAMPION	Oct 2020-present	3000	200	Ongoing

In the PILOT study, the WATCHMAN Device was successfully implanted in 66/75 (88%) subjects, with discontinuation of warfarin in 68% of subjects at 45 days, 92% of subjects by six months, and 96% of subjects by 60 months. Mean follow-up in this study was 6.1 years. There were no deaths, no device embolizations related to the Closure Device, and no evidence of long-term erosion. These results supported progression to a pivotal study.

The first pivotal study, WATCHMAN Left Atrial Appendage System for Embolic PROTECTion in Patients with Atrial Fibrillation[14] (PROTECT- AF), demonstrated non-inferiority of the WATCHMAN Device to long-term warfarin therapy for the primary effectiveness endpoint of stroke, systemic embolism, and cardiovascular death.

The published analysis of the PROTECT AF[15] trial has shown that the WATCHMAN Device achieved superiority for the combined endpoint of all stroke, cardiovascular or unexplained

death and systemic embolism (for Bayesian analysis, posterior probabilities are used to determine superiority; > 95% represents superiority).

- The observed primary effectiveness event rate was 2.3 percent and 3.8 percent in the WATCHMAN and control groups, respectively, demonstrating a 40% percent relative risk (RR) reduction in primary effectiveness in the WATCHMAN group (RR = 0.60, posterior probability of superiority = 96 percent%).

Secondary analysis also showed a relative risk reduction and superiority to control for all-cause mortality and cardiovascular mortality.

- All-Cause Mortality: the WATCHMAN group was superior to the control group, 3.2% percent to 4.8 percent % respectively, representing a 34 percent% relative risk reduction in all-cause mortality in the WATCHMAN group (Hazard ratios [HR] = 0.66, p=0.0379).
- Cardiovascular Mortality: the WATCHMAN group was superior to the control group, 1.0 percent% and 2.4 percent % respectively, representing a 60 percent% relative risk reduction in cardiovascular death in the WATCHMAN group (HR = 0.40, p=0.0045).

The Continued Access to PROTECT Registry[16](CAP Registry) provided continued access of the WATCHMAN Device to PROTECT- AF investigators and demonstrated a decrease in procedural complications of pericardial effusion with tamponade, cardiac perforation, and device embolization (1.2%, 0.2%, 0%, respectively).

The ASA Plavix Study with WATCHMAN Left Atrial Appendage Closure Technology (ASAP) study was a multi-center, prospective non-randomized study of 150 subjects enrolled at four sites in Europe. Subjects were followed post-implant at 3, 6, 12, 18, and 24 months. The primary objective of this study was to characterize the performance of the WATCHMAN Left Atrial Appendage (LAA) Closure Device in non-valvular atrial fibrillation subjects for which warfarin therapy was contraindicated. The overall results from the ASAP study demonstrated the following:

- Ischemic stroke was reported in 3 subjects for a rate of 1.7 per 100 pt.-yrs. This rate is significantly lower than other trials assessing stroke rates in subjects with atrial fibrillation who are unable to take anticoagulant therapy.
- All stroke and ischemic stroke rates in the ASAP study were similar to those observed in the randomized non-inferiority PROTECT AF study with subjects eligible for warfarin therapy. In PROTECT AF, the rates of all-cause death, all stroke, and ischemic stroke were 3.0, 2.3, and 2.2 events per 100 pt-yrs, respectively. In the ASAP study rates for death, all stroke, and ischemic stroke were 5.1, 2.3, and 1.7 events per 100 pt-yrs, respectively. These rates are comparable despite subjects in ASAP having a higher $CHADS_2$ stroke risk (2.8 vs. 2.2 in PROTECT AF).
- Implant of the WATCHMAN device can be safely performed in subjects with contraindications to warfarin therapy[17].

The second pivotal study, Prospective Randomized Evaluation of the WATCHMAN LAA Closure Device In Patients with Atrial Fibrillation Versus Long Term Warfarin Therapy (PREVAIL), was conducted to provide additional information on the implant procedure and complication rates associated with the device. [18]In this trial, LAA occlusion was non-inferior to warfarin for ischemic stroke prevention or systemic embolism (SE) >7 days' post-procedure. Although non-inferiority was not achieved for overall efficacy, event rates were low and numerically comparable in both arms. Procedural safety has significantly improved over the previous trials, PROTECT AF and CAP. PREVAIL only data, data from subjects enrolled in the PREVAIL study without the prior PROTECT AF study information used in the Bayesian analysis, showed that the ischemic stroke rate (1.67 vs. 0.73 per 100 pt.-years) favored to the Control group, while the hemorrhagic stroke rate (0.18 vs. 0.54 per 100 pt.-years) and death (cardiovascular or unexplained) rate (1.88 vs. 1.98 per 100 pt.-years) favored the WATCHMAN group. The PREVAIL trial provides additional data that LAA occlusion is a reasonable alternative to warfarin therapy for stroke prevention in patients with NVAF who do not have an absolute contraindication to short-term warfarin therapy.[19]

The Continued Access Protocol (CAP2) was a prospective, non-randomized, multicenter study to allow continued access to the WATCHMAN LAA Closure Technology during the data analysis, reporting and review of the PREVAIL pivotal study Pre-Market Application by FDA. The first of 578 subjects were enrolled on 25-Sep-2012. The final subjects were enrolled on 21-Mar-2014 and have completed 5 years of follow-up. Subjects in this trial were at a high-risk of stroke with a mean CHA_2DS_2-VASc of 4.5 (+/- 1.3). Additionally, 98% were at moderate to high risk of bleeding. Patients in this trial had an ischemic stroke rate of 2.2 per 100 patient-years, which is in line with the other WATCHMAN trials.[20]

The purpose of the EValuation of the Next Generation WATCHMAN LAA Closure TechnOLogy in Non-Valvular AF PatiEnts (EVOLVE) study was to evaluate the implantability of the Gen 4 WATCHMAN LAA Closure Device in patients with non-valvular atrial fibrillation (AF) with a $CHADS_2$ stroke risk stratification of 1 or greater. The primary objectives of the study were to assess successful delivery and release of the WATCHMAN (Gen 4) Closure Device, the occurrence of serious pericardial effusions and the discontinuation of warfarin at 45 days. Patients who had non-valvular paroxysmal, persistent, or permanent AF, had a $CHADS_2$ score of $\geq$1, and were eligible for warfarin therapy were screened as candidates for the study and implant.

In the EVOLVE study, the successful delivery and release of the WATCHMAN Gen 4 Closure Device and the occurrence of serious pericardial effusions were either consistent with or an improvement upon the results from the PROTECT AF study. Therefore, the acute objectives of the study were met and demonstrate pericardial effusion and device recapture rates lower than that seen with the Gen 2.5 Device in PROTECT AF. This demonstrates that the Gen 4 WATCHMAN LAA Closure Device could be safely implanted in patients with non-valvular atrial fibrillation (AF) with $CHADS_2$ stroke risk score of 1 or greater. The closed distal end of this generation device was similar to WATCHMAN FLX, however, for business purposes, the commercialization of the Gen 4 device was not pursued in lieu of developing WATCHMAN FLX.

The REgistry on WATCHMAN Outcomes in Real-Life Utilization (EWOLUTION) study was an observational, prospective, single-arm, multicenter clinical study (Europe, Middle East, Russia) that compiled real-world clinical outcome data for WATCHMAN LAA Closure Device in a commercial setting and collected health care usage data for reimbursement decisions in certain countries; EWOLUTION continues to build on the existing WATCHMAN clinical database. EWOLUTION is a purely observational post-market data collection study. Consecutive enrollment was strongly encouraged, and achieved in most sites, to minimize selection bias and maintain the strengths of a large-scale, all-comers clinical registry. A total of 1020 patients scheduled for a WATCHMAN implant at 47 centers in 13 countries were enrolled, and subjects were followed for two years after WATCHMAN implantation according to standard medical practice. Analyses included procedural and long-term data, including stroke/embolism, bleeding, and death.[21-23]

Baseline/implant data, the results of the peri-procedural analyses, and data through the first annual visit were presented for the 1020 subjects who underwent the implant procedure.[22-23] The EWOLUTION population was at high risk for stroke presenting with $CHADS_2$ (2.8±1.3) and CHA_2DS_2-VASc (4.5±1.6) scores. The population had a moderate-to-high risk of bleeding with an average HAS-BLED score: 2.3 ± 1.2. Approximately 72% of patients in EWOLUTION were deemed unsuitable for OAC by their physician. The device was successfully deployed in 98.5% of patients with no or minimal residual flow achieved in 99.8% of implanted patients. There were twenty-six (2.8%, 1.6–3.6%) serious adverse events occurring in 23 subjects reported as relating to the procedure at 7 days. Eighteen were considered Major Cardiac Events (1.8%). There was one case of death as a consequence of an air embolism during the implant procedure. Three additional deaths within 7 days appear unrelated to the device. These rates of procedural success and 7-day device-related SAEs were lower than those found in PROTECT AF, CAP, PREVAIL, and CAP2.

The annual rate of ischemic stroke was 1.3/100 pt.-years, which translates into an 84% risk reduction, as compared with the calculated stroke rate of 7.2/100 pt.-years in the absence of stroke preventive therapy for similar CHA_2DS_2-VASc scores. There were no occurrences of periprocedural strokes and no fatal strokes in the study. Combining ischemic stroke with TIA and systemic thromboembolism, the annual rate is 2.0/100 pt.-years, translating into an 80% risk reduction as compared to the expected rate of 10.1//100 pt.-years based on CHA_2DS_2-VASc scores. Major bleeding (which includes fatal and life threatening) aligns with the LAAC-specific modifications and refinements described by Tzikas et al. in the consensus document on definitions, endpoints and data collection requirements. Intracranial bleeding and cardiac tamponade are always considered major bleeding without further assessment criteria. The annual rate of major bleeding in the study was 3.3/100 pt.-years, which corresponds to a 34% risk reduction, as compared with the rate of 5.0//100 pt.-years that would be expected under VKA therapy based on a comparable HAS-BLED score. The majority of the bleeding events occurred outside the periprocedural period. The rate of major bleeding events, excluding procedural bleedings, is 2.7/100 pt.-years, which corresponds to a 46% reduction as compared with the expected rate of 5.0/100 pt.-years based on HAS-BLED score.

The WATCHMAN ASia Pacific Registry (WASP) is an Asia/Pacific registry with identical design to EWOLUTION that compiles real-world clinical outcome data for the WATCHMAN LAA Closure Device in a commercial setting and collects health care usage data for reimbursement decisions in certain countries. Like EWOLUTION, WASP is a purely observational post-market data collection study. Results are in line with the larger EWOLUTION study: successful implantation occurred in 98.5% of patients; 7-day device/procedure-related SAE rate was 3.0%. After 2 years of follow-up the rates of ischemic stroke/TIA/systemic embolism and major bleeding were 1.9 and 2.3 per 100-PY, respectively, representing relative reductions of 77% and 49% versus expected rates per risk scores[24].

The WATCHMAN New Enrolment Post-Approval Surveillance Analysis Plan (NESTed SAP) is designed to assess long-term safety and effectiveness outcomes associated with the use and implantation of the WATCHMAN Left Atrial Appendage (LAA) Closure Technology in a routine clinical setting. This is an analysis plan that will utilize data collected by the ACCF's LAAO Registry. All data analysed will be from patients receiving a Boston Scientific Corporation WATCHMAN device at hospitals participating in the LAAO Registry. As part of regulatory requirements, the WATCHMAN NESTed SAP will collect device safety and effectiveness data on 2,000 patients enrolled in the LAAO Registry. Since the NESTed SAP leverages LAAO Registry patient data, patient data elements collected for the NESTed SAP will be identical to those collected for LAAO Registry patients.

The primary cohort data of 1000 subjects have been reported. Compared with previous trials and registries (Figure), the patients were older and had higher baseline stroke and bleeding risks (mean age 76.5±8.1, CHA2DS2-VASc 5.0±1.4, HAS-BLED 2.7±1.0, 38% female). The composite primary safety endpoint event rate of 1.49% compares favorably to the rates observed in prior trials. The upper 95% confidence interval for the primary safety endpoint (2.32%) was below the pre-specified threshold (3.36%). Thus, procedural safety results from the US NESTed Post-approval study are consistent with prior clinical studies in a higher risk population. Continued clinical outcomes surveillance will guide LAAO as an option for high-risk patients with non-valvular atrial fibrillation who have reasons to seek an alternative to oral anticoagulation[25].

SALUTE is a study to evaluate the SAfety and effectiveness of the Left atrial appendage closure therapy for patients with non-valvUlar atrial fibrillation at increased risk of ThromboEmbolism. This study was conducted in Japan; enrollment and long-term follow-up are complete. A total of 54 subjects (including 12 Roll-in) with NVAF who had a CHA2DS2-VASc score ≥2 were enrolled. All 42 subjects in the intention to treat (ITT) cohort underwent successful implantation of the LAAC device without any serious complications, achieving the prespecified performance goal. The effective LAAC rate was maintained at 100% from 45 days to 12 months post-implant, achieving the prespecified performance goal. During follow-up, 1 subject died of heart failure, and 3 had ischemic non-disabling strokes, but there were no cases of hemorrhagic stroke or systemic embolism. The final results of the SALUTE trial demonstrated that the WATCHMAN LAAC device is an effective and safe alternative nonpharmacological therapy for stroke risk reduction in Japanese NVAF patients who are not optimal candidates for lifelong anticoagulation[26]

The Assessment of the WATCHMAN™ Device in Patients Unsuitable for Oral Anticoagulation (ASAP-TOO) Study is designed to establish the safety and effectiveness of the WATCHMAN™ Left Atrial Appendage Closure Device, including the post-implant medication regimen, for subjects with non-valvular atrial fibrillation who are deemed not to be eligible for anticoagulation therapy to reduce the risk of stroke. The device is intended to reduce the risk of thromboembolic ischemic stroke and systemic embolism. Enrollment started in February 2017 and was terminated October 15, 2020 due to slow enrollment with a total of 481 randomized subjects. Follow up is ongoing.

PINNACLE FLX is a prospective, non-randomized, multi-center investigation to establish the safety and efficacy of the WATCHMAN FLX LAAC Device. The trial has completed enrollment of the 400 subjects required for the primary analyses and follow-up is complete. The mean age was 73.8 ± 8.6 years and the mean CHA2DS2-VASc score was 4.2 ± 1.5. The incidence of the primary safety endpoint (occurrence of either death, ischemic stroke, systemic embolism, or device- or procedure-related events requiring cardiac surgery within 7 days post-procedure or by hospital discharge, whichever was later) was 0.5% with a one-sided 95% upper confidence interval (CI) of 1.6%, meeting the performance goal (PG) of 4.2% ($P<0.0001$). The incidence of the primary effectiveness endpoint (effective LAA closure (peri-device flow ≤5 mm) at 12 months) was 100%, with a one sided 95% lower CI of 99.1%, again meeting the PG of 97.0% ($P<0.0001$). Device-related thrombus was reported in 7 patients, no patients experienced pericardial effusion requiring open cardiac surgery, and there were no device embolizations. LAA closure with this next generation LAA closure device was associated with a low incidence of adverse events and a high incidence of anatomic closure.[27]

FLXibility is a European prospective, non-randomized, multi-center investigation designed to collect real-world clinical outcome data for patients who are implanted with the WATCHMAN FLX device in a commercial clinical setting according to its labelling (post-market, standard of care study). The purpose of FLXibility is to provide additional evidence of the safety and performance of the device. The trial completed enrollment in July 2020 and follow-up is ongoing.

I Can sEe Left Atrial Appendage (ICE LAA) Clinical Study is a prospective, non-randomized, single-arm, multi-center investigation to assess the use of ICE to guide WATCHMAN FLX implants for subjects with non-valvular atrial fibrillation to reduce the risk of stroke. Approximately 100 subjects will be followed through the enrollment period, at device implant, then at intervals of 45 days. The primary objective of this study is to assess the use of intracardiac echocardiography (ICE) imaging of the Left Atrial Appendage during WATCHMAN FLX Left Atrial Appendage Closure (LAAC) implant procedure for subjects with non-valvular atrial fibrillation. This study has completed enrollment and follow up.

The CHAMPION study is a prospective, randomized, multi-center global investigation to determine if left atrial appendage closure with the WATCHMAN FLX Device is a

reasonable alternative to NOACs in patients with non-valvular atrial fibrillation. A maximum of 3000 subjects will be followed through the enrollment period, at device implant, then at intervals of 90 days, 120 days (LAA imaging), 12 months, 24 months, 36 months, 48 months and 60 months. The primary objective of this study is to determine if left atrial appendage closure with the WATCHMAN FLX device is a reasonable alternative to non-vitamin K oral anticoagulants (NOACs) in patients with non-valvular atrial fibrillation. This study is currently enrolling.

4.3. *Study Rationale*

LAA closure with a WATCHMAN Device is currently used in patients who are considered poor candidates for long-term OAC; however, patients who undergo AF catheter ablation procedures and are at risk for stroke are not necessarily deemed poor candidates for OAC unless other factors exist (i.e., factors unrelated to the AF catheter ablation procedure). OPTION is designed to determine if left atrial appendage closure with the WATCHMAN FLX Device is a reasonable alternative to oral anticoagulation following percutaneous catheter ablation for non-valvular atrial fibrillation.

5. Device Description

The WATCHMAN FLX Delivery System consists of the Delivery Catheter and the pre-loaded Closure Device, Figure 1. The WATCHMAN FLX Delivery System is used in conjunction with a WATCHMAN Access System. Together, the WATCHMAN Access System and WATCHMAN FLX Delivery System permit device placement in the LAA via femoral venous access and crossing the inter-atrial septum into the left atrium. The WATCHMAN Access System is commercially available and a required accessory for use with the WATCHMAN FLX procedures. The WATCHMAN TruSeal Access System is commercially available in select geographies and is compatible with the WATCHMAN FLX Delivery System. If additional generations of the WATCHMAN Access Systems become commercially available during the enrollment phase of the study, these Access Systems may be used in OPTION.

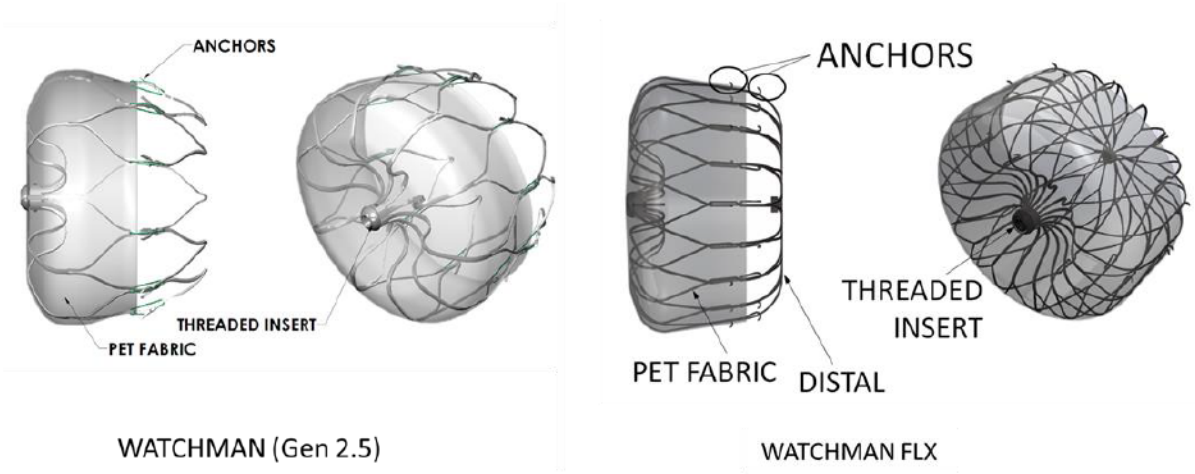
5.1.1. *WATCHMAN FLX Delivery System and with Pre-loaded LAAC Device*

The Delivery Catheter for WATCHMAN FLX consists of an inner core wire with a reinforced braided jacket that is connected to the deployment knob at the proximal end and a screw thread assembly at the distal end. The outer sheath has an overall profile of 12F.

The WATCHMAN FLX Device is pre-loaded into a Delivery Catheter and is deployed by loosening the valve on the Delivery System and retracting the outer sheath. The WATCHMAN FLX Device can be partially recaptured and redeployed if the device is too distal. If the Closure Device is deployed too proximal, it can be fully recaptured. The WATCHMAN FLX Device has the added ability over the existing WATCHMAN (Gen 2.5) device to be redeployed after being fully recaptured. As with the existing WATCHMAN Device, the Closure Device is released by rotating the device deployment knob counter clockwise.

The WATCHMAN FLX Device is comprised of a self-expanding nitinol frame structure with fixation anchors around the Closure Device perimeter and a permeable polyester fabric that covers the atrial facing surface of the Closure Device. The Closure Device is constrained within the Delivery Catheter until deployment in the LAA. The WATCHMAN FLX Device is available in 5 sizes, from 20 to 35 mm. It is similar to the currently available WATCHMAN (Gen 2.5) Device, but covers a slightly larger range of appendage ostium diameters, from 14 to 31.5 mm. Appropriate Closure Device sizing is determined by LAA measurements using fluoroscopy (fluoro) and echocardiographic guidance.

Figure 1: WATCHMAN Delivery System (Delivery Catheter & LAA Closure Device)



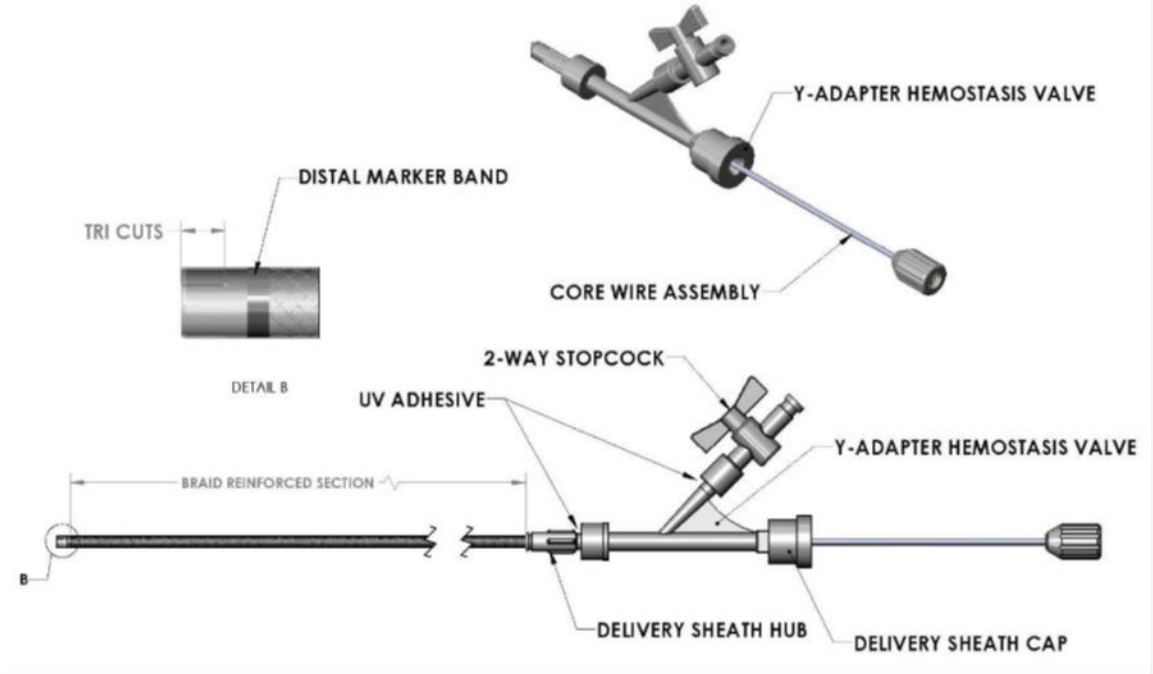
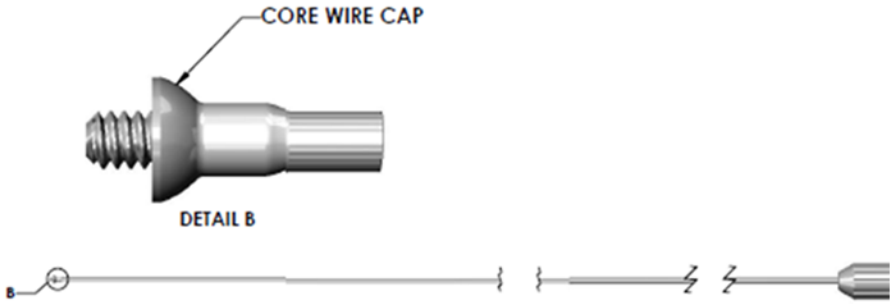


Illustration of WATCHMAN FLX Delivery Sheath Assembly



- Illustration of WATCHMAN FLX Core Wire

Similar to the previous WATCHMAN Devices, the WATCHMAN FLX Device is designed to be permanently implanted at or slightly distal to the ostium (opening) of the LAA to trap potential emboli before they exit the LAA. The placement procedure can be done under local or general anesthesia in a catheterization laboratory.

In addition, WATCHMAN FLX incorporates the following novel features to enhance the user experience for the WATCHMAN LAA Closure Technology compared to the existing WATCHMAN Closure Device with Delivery System:

- Closed Distal End – Provides improved deployment stability and control, with atraumatic distal structure.
- Fully Recapturable and Redeployable – Designed to decrease the number of devices used and sheath exchanges per case, which may reduce procedure time and complications associated with sheath exchange.

- Decreased Recapture Force – Designed to improve user experience.
- Increased Conformability – Designed to create better left atrial appendage seal due to the increased number of contact points around the LAA ostium, designed to promote short-term healing.
- Decreased Exposed Metal Volume on Proximal Face – May promote short-term healing.
- Enhanced Radiopacity – Designed to improve visibility under fluoroscopy.
- Smaller and Larger Device Size – Designed to allow for treatment of complex, shallow LAA anatomies.
- Greater Overlap in Device Sizing Choices – Designed to allow for treatment of a wider range of appendage sizes.

5.1.2. *WATCHMAN Access System and WATCHMAN TruSeal Access System (Access Sheath and Dilator)*

The 14F (12F ID) transseptal Access Sheath for both the WATCHMAN Access System and WATCHMAN TruSeal Access System is utilized to gain access to the LAA and serves as a conduit for the WATCHMAN FLX Delivery System. The distal end of the Access Sheath is available in three curve styles to assist with placement of the sheath into the LAA. The various curve styles allow for coaxial placement of the sheath into the LAA. The distal tip contains a marker band for in situ visualization as well as sizing marker bands used to gauge if the Access Sheath is positioned at the appropriate depth in the LAA based on the device size selected.

The Access Sheath and Dilator are utilized to gain access to the LAA after initial transseptal access into the left atrium has been established. Once the Access Sheath is positioned into the left atrium and the Dilator has been removed, the Access Sheath then serves as a conduit for the Delivery System. The Delivery System is introduced into the Access Sheath and the components snap together to act as one during device implantation.

WATCHMAN TruSeal Access System, which uses an identical dilator to the WATCHMAN Access System, is an enhanced next-generation Access System to replace the existing matrix of the WATCHMAN Access System. The WATCHMAN TruSeal Access System is compatible with all commercially available WATCHMAN Left Atrial Appendage Closure Devices with Delivery Systems.

Investigators should have experience using the WATCHMAN FLX Device and TruSeal Access System, prior to utilizing them together in the trial.

Figure 2: WATCHMAN Access System

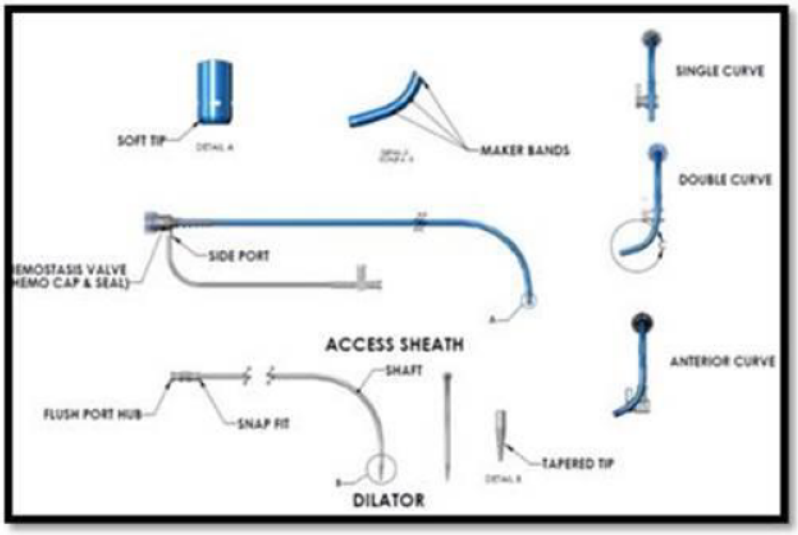
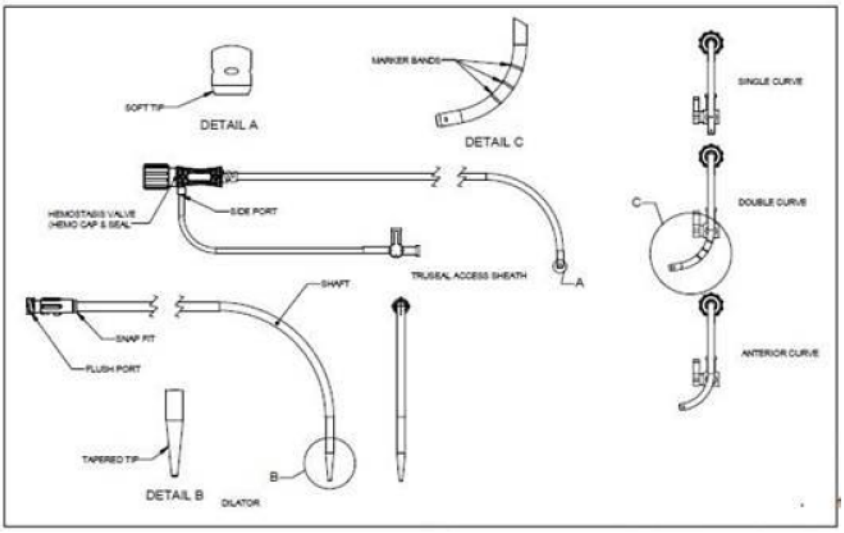


Figure 3: WATCHMAN TruSeal Access System



5.1.3. *Indications for Use*

The planned indication for use within the OPTION study is as follows:
The WATCHMAN and WATCHMAN FLX Device are indicated to reduce the risk of thromboembolism from the left atrial appendage in subjects with non-valvular atrial fibrillation who:

- Are at increased risk for stroke and systemic embolism based on CHA_2DS_2-VASc scores following catheter ablation of atrial fibrillation; and
- Are deemed suitable for anticoagulation therapy

Note: In countries where CE mark applies, the OPTION indication is within the CE mark approved Indication for Use.

6. Study Objective

The primary objective of this study is to determine if left atrial appendage closure with the WATCHMAN FLX Device is a reasonable alternative to oral anticoagulation following percutaneous catheter ablation for non-valvular atrial fibrillation.

7. Study Endpoints

7.1. *Primary Effectiveness Endpoint*

WATCHMAN therapy is non-inferior for the occurrence of stroke (including ischemic and/or hemorrhagic), all cause death, and systemic embolism at 36 months. This endpoint is defined as the Kaplan Meier estimate of time to first occurrence of stroke (including ischemic and/or hemorrhagic), all cause death, or systemic embolism at 36 months.

7.2. *Primary Safety Endpoint*

WATCHMAN therapy is superior for non-procedural bleeding through 36 months (ISTH major bleeding and clinically relevant non-major bleeding). This endpoint is defined as the Kaplan Meier estimate of time to first occurrence of non-procedural ISTH major bleeding or clinically relevant non-major bleeding through 36-months.

7.3. *Secondary Endpoint*

WATCHMAN therapy is non-inferior for ISTH major bleeding at 36 months (including procedural bleeding). This endpoint is defined as the Kaplan Meier estimates of time to first occurrence of major bleeding at 36 months.

7.4. *Additional Analyses*

1. The occurrence and incidence of:

- Stroke
  - Ischemic stroke
  - Hemorrhagic stroke
  - Disabling stroke
  - Non-disabling stroke
- Systemic embolism
- Procedural and non-procedural bleeding and classifications; ISTH major bleeding and clinically relevant non-major bleeding
- All-cause death
  - Cardiovascular/unknown death
  - Non-cardiovascular death
- Device related Thrombus

2. Device success (Device deployed and implanted in correct position)
3. Rates of effective (defined as jet size of ≤5mm) and complete (defined as no peri-device flow) LAA closure at 3- and 12-months post implant
4. Freedom from AF (see section 13 for definition)
5. Healthcare resource utilization
6. Quality of life

8. Study Design

This study is a prospective, randomized, multi-center, global investigation to determine if left atrial appendage closure with the WATCHMAN FLX Device is a reasonable alternative to oral anticoagulation in patients after percutaneous ablation of non-valvular AF.

Implanting investigators will include physicians who have WATCHMAN (Gen 2.5) and/or WATCHMAN FLX implant experience. The WATCHMAN FLX implanting investigator does not have to be the same physician performing ablation within the trial. All implanting physicians must have completed WATCHMAN FLX implant training. All sites without WATCHMAN FLX experience (i.e., have implanted ≥ 2 WATCHMAN FLX devices commercially or within the PINNACLE FLX IDE) will be required to implant two Roll-in subjects prior to implanting in the main cohort of subjects. Roll-in subjects will be declared prior to implant, must be completed prior to implanting in the main randomized cohort, and must meet all protocol requirements.

Sites will be limited to two WATCHMAN FLX implanting investigators per institution in geographies where the device is investigational.

Note: While the device is considered investigational in the United States, sites who participated in the PINNACLE FLX trial and who had two trained WATCHMAN FLX implanting physicians in that study may add one additional implanting physician for the OPTION study.

Percutaneous catheter ablation using currently available non-surgical standard techniques and market-approved technology may be performed at the time of the WATCHMAN FLX implant procedure **only for Concomitant Ablation subjects**

- The procedures must occur on the same day with the ablation occurring prior to the WATCHMAN FLX implant.
- Catheter ablation of the LAA, non-standard ablation techniques (e.g., CFAEs and hybrid ablation) and any non-AF-related ablation (e.g., VT) are not permitted.
- Other concomitant procedures are also not permitted, including, but not limited to, transcutaneous valve procedures, pacemaker, or ICD generator change, etc.

Note: Sequential Ablation subjects who need a repeat ablation cannot combine it with the WATCHMAN FLX implant procedure.
For all patients, CTI ablation and cardioversion may be performed during ablation.

8.1. *Scale and Duration*

A maximum of 1600 subjects will be randomized in the study at a maximum of 150 global sites. A maximum of 260 additional patients will be treated in the roll-in phase of the study.

The duration of the study is expected to last approximately 64 months. The duration of individual subject participation is expected to last approximately 36 months but may vary per subject.

Given the number of sites that have PINNACLE FLX experience, and the total number of planned sites, it is expected that the number of roll-ins in the United States will be approximately 130.

8.2. *Treatment Assignment*

A subject who signs informed consent is considered enrolled in the study. Subjects will be randomized to OAC or WATCHMAN FLX in equal proportion. Randomization will be stratified by sequential vs. concomitant planned ablation +/- WATCHMAN implantation, to help ensure balance of treatment assignments within the sequential and concomitant groups. The planned ablation procedure type, concomitant or sequential, must be specified prior to randomizing the subject.

8.2.1. Device Group Treatment

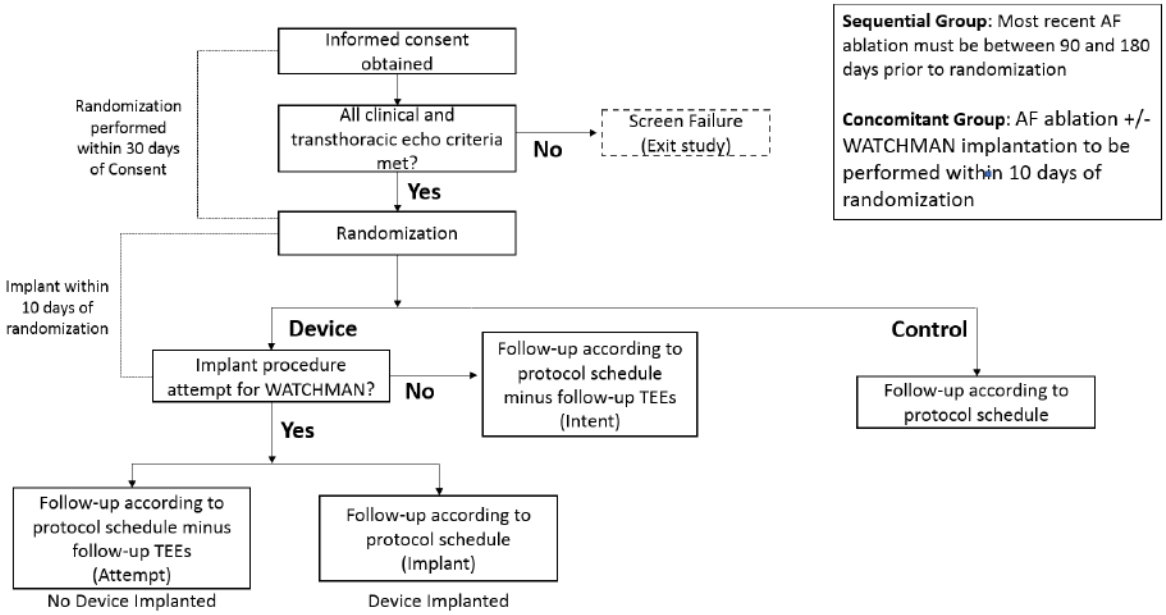
Subjects randomized to the device group will be implanted with the WATCHMAN FLX device. WATCHMAN FLX is available in 20, 24, 27, 31, and 35mm models to fit left atrial appendage ostia widths ranging from 14.0 - 31.5mm.

After the WATCHMAN FLX implant, Device Group subjects will be prescribed market-approved OAC and aspirin (75-100mg recommended) until the 3-month visit followed by aspirin until at least the 12-month visit (recommended for duration of the trial).

8.2.2. Control Group Treatment

Following randomization, control subjects must continue or start market approved OAC used per IFU for atrial fibrillation stroke prevention and should remain on it for the duration of the trial.

Figure 4: Study Flow Diagram



Note: for Roll-ins subjects windows are calculated from implant date, instead of randomization date

8.3. *Justification for the Study Design*

Patients undergoing AF ablation are not only seeking symptom relief from the arrhythmia, but also pursuing stroke prevention. Ablation alone has not been proven in randomized clinical trials to prevent stroke, and current societal guidelines recommend for patients with a CHA_2DS_2-VASc of 2 or greater to continue their oral anticoagulation indefinitely[18]. Recently, LAAC has been shown to be similar to OAC in subjects with CHA_2DS_2-VASc $\geq$ 2 and a rationale to seek an alternative to OAC. This study is designed to determine if left atrial appendage closure with the WATCHMAN FLX Device is a reasonable alternative to oral anticoagulation following percutaneous catheter ablation for non-valvular atrial fibrillation.

9. Subject Selection

9.1. *Study Population and Eligibility*

Study inclusion and exclusion criteria are included below in sections 9.2 and 9.3.

9.2. *Inclusion Criteria*

Subjects who meet all of the following criteria (see Table 9.2-1) may be given consideration for inclusion in this clinical investigation, provided no exclusion criterion (see Section 9.3 and Section 9.4) is met.

Table 9.2-1: Inclusion Criteria

Inclusion Criteria	1. The subject is of legal age to participate in the study per the laws of their respective geography. 2. Underwent a prior catheter ablation procedure for non-valvular AF between 90 and 180 days prior to randomization (sequential) or is planning to have clinically indicated catheter ablation within 10 days of randomization (concomitant). 3. The subject has a calculated CHA2DS2-VASc score of 2 or greater for males or 3 or greater for females. 4. The subject is deemed by the treating physician to be suitable for the protocol defined pharmacologic regimens. 5. The subject is able to undergo TEE examinations. 6. The subject or legal representative is able to understand and is willing to provide written informed consent to participate in the trial. 7. The subject is able and willing to return for required follow-up visits and examinations.

9.3. *Exclusion Criteria*

Subjects who meet any one of the following exclusion criteria (Table 9.3-1) will be excluded from this clinical study.

Table 9.3-1: Exclusion Criteria

Exclusion Criteria	1. The subject is currently enrolled in another investigational study that would directly interfere with the current study, except when the subject is participating in a mandatory governmental registry, or a purely observational registry with no associated treatments. Each instance must be brought to the attention of the sponsor to determine eligibility, regardless of type of co-enrollment being proposed. 2. The subject requires long-term anticoagulation therapy for reasons other than AF-related stroke risk reduction, for example due to an underlying hypercoagulable state (i.e., even if the device is implanted, the subjects would not be eligible to discontinue OAC due to other medical conditions requiring chronic OAC therapy). 3. The subject is deemed by the treating physician to be unsuitable for chronic anticoagulation and/or aspirin therapy due to bleeding risk, allergy, or other reasons. 4. The subject had or is planning to have any cardiac or major non-cardiac interventional or surgical procedure (excluding non-valvular AF ablation and cardioversion) within 30 days prior to or 60 days after randomization [including, but not limited to: percutaneous coronary intervention (PCI), other cardiac ablation (VT ablation, etc.), etc.]. 5. The subject had a stroke or transient ischemic attack (TIA) within the 60 days prior to randomization. 6. The subject had a prior major bleeding event per ISTH definition within the 14 days prior to randomization. Lack of resolution of related clinical sequelae or planned and pending interventions to resolve bleeding/bleeding source, are a further exclusion regardless of timing of the bleeding event. 7. The subject has had a myocardial infarction (MI) documented in the clinical record as either a non-ST elevation MI (NSTEMI) or as an ST-elevation MI (STEMI), with or without intervention, within 90 days prior to randomization. 8. The subject has a history of atrial septal repair or has an ASD/PFO device. 9. The subject has an implanted mechanical valve prosthesis in any position. 10. The subject is of childbearing potential and is, or plans to become pregnant during the time of the study (method of assessment upon study physician's discretion) 11. The subject has a documented life expectancy of less than two years. 12. The subject has a cardiac tumor. 13. The subject has signs/symptoms of acute or chronic pericarditis. 14. There is evidence of tamponade physiology. 15. The subject has contraindications (anatomical or medical) to percutaneous catheterization procedures. 16. The subject has documented NYHA Class IV heart failure. 17. The subject has documented surgical closure of the left atrial appendage. 18. The subject has an active infection.

9.4. *Transthoracic Echocardiographic Exclusion Criteria*

After signature of the informed consent and prior to randomization all enrolled subjects will undergo a transthoracic echocardiographic evaluation to further confirm eligibility. Subjects who meet any one of the following echo exclusion criteria (Table 9.4-1) will be excluded from this clinical study and must not be randomized. The baseline TTE will be done to evaluate all exclusion criteria to confirm subject eligibility. Criteria obtained from cardiac imaging performed within 180 days prior to randomization may be used if all the exclusion criteria can be evaluated. If all exclusion criteria were not obtained on the prior cardiac imaging, a TTE will have to be conducted at baseline. If a significant cardiac event occurs after the cardiac imaging which causes a change in cardiac status [i.e., major Congestive Heart Failure (CHF) decompensation] the baseline TTE must be repeated after informed consent and prior to randomization.

Table 9.4-1: Transthoracic Echo Exclusion Criteria

Transthoracic Echo Exclusion Criteria	1. The subject has LVEF < 30% 2. The subject has an existing pericardial effusion with a circumferential echo-free space > 5mm. 3. The subject has a high- risk patent foramen ovale (PFO) with an atrial septal aneurysm excursion > 15mm or length > 15mm. 4. The subject has a high-risk PFO with a large shunt defined as early, within 3 beats and/or substantial passage of bubbles. 5. The subject has significant mitral valve stenosis (i.e., MV area <1.5 cm^2).

10. Subject Accountability

10.1. *Point of Enrollment*

The point of enrollment is the time at which a subject signs and dates the informed consent form (ICF). No study specific tests, procedures, etc. can take place until the ICF is signed. Subjects that are determined to not meet clinical or echo eligibility criteria after signing consent, and prior to randomization, will be considered screening failures and will not count towards the enrollment ceiling.

Subjects may be re-enrolled at a future date under a new subject ID if it is determined that the reason the subject screen failed no longer applies.

10.2. *Subject Status and Classification*

10.2.1. Screen Failure

A subject who has a valid and signed informed consent but is not randomized is considered a screen failure. ***Screen failure subjects do not count towards the enrollment ceiling and will not be used for the primary analyses***. Screen failure subjects should be exited immediately upon determining their ineligibility. The original signed informed consent must be

maintained in the site's subject file and the following forms must be completed for all information collected prior to determining the subject's ineligibility:

- Baseline forms such as, but not limited to: informed consent, baseline information, and other related forms up to the point of screen fail
- "Adverse Event" form(s) for any reportable event, as defined in **Section 21**, for any adverse event that occurs after signing the informed consent, up to the point of screen fail

10.2.2. Randomized

Prior to randomization, the planned ablation procedure type, concomitant or sequential, must be specified. A randomized subject is a subject who signs informed consent and is randomized. Subjects must not be randomized unless they have a valid and signed informed consent and meet all inclusion and no exclusion criteria.

For subjects in the sequential group, randomization can only occur between 90 and 180 days following the most recent AF ablation procedure. Subjects who are planning to have a concomitant procedure must be randomized within 10 days prior to the planned ablation procedure. All subjects (concomitant or sequential) randomized to the Device Group are required to undergo WATCHMAN FLX Device implant within 10 calendar days of randomization. Both groups are followed in accordance with the follow-up schedule. All applicable case report forms per the protocol must be completed. The original signed informed consent and any relevant documentation must be maintained in the site's subject file.

10.2.3. Device Group Classifications

Subjects randomized to the Device Group and Roll-In subjects will be further classified as either an intent, attempt, or implant. After study enrollment completion, if the classification is to be updated by the site, the site will contact the study team directly for further instruction.

10.2.3.1. Intent

A Randomized subject in the Device Group that does not have an implant attempt (i.e., WATCHMAN Access Sheath is never inserted into the body) will be classified as an "Intent" subject. The reason for the Intent will be collected in the database. Intent subjects count towards the enrollment ceiling and will be used for analyses of the endpoints according to intention-to -treat principles. Intent subjects will be followed according to the follow-up schedule with the exception of the follow-up LAA imaging. Intent subjects are not required to have the 3-month and 12-month follow-up LAA imaging. Intent subjects are not required to follow the Device Group medication requirements, but antiplatelet, NSAIDs, anticoagulant, and antiarrhythmic medications must be captured in the medication logs. All applicable case report forms per the protocol must be completed. The original signed informed consent and any relevant documentation must be maintained in the site's subject file.

10.2.3.2. Attempt

A Randomized subject in the Device Group that has had the WATCHMAN Access Sheath inserted into the body in order to implant the device, but eventually does not receive a WATCHMAN FLX Device will be classified as "Attempt." Attempt subjects count towards the enrollment ceiling and will be used for analyses of the endpoints according to intention-to-treat principles. Attempt subjects will be followed according to the follow-up schedule with the exception of the follow-up LAA imaging. Attempt subjects are not required to have the 3-month and 12-month follow-up LAA imaging. Attempt subjects are not required to follow the Device Group medication requirements, but antiplatelet, NSAIDs, anticoagulant, and antiarrhythmic medications must be captured in the medication logs. All applicable case report forms per the protocol must be completed. The original signed informed consent and any relevant documentation must be maintained in the site's subject file.

10.2.3.3. Implant

A subject who is successfully implanted with the WATCHMAN FLX Device will be classified as an "Implant." These subjects are followed in accordance with the follow-up schedule. All applicable case report forms per the protocol must be completed. The original signed informed consent and any relevant documentation must be maintained in the site's subject file.

10.3. *Study Completion, Withdrawal, or Lost to Follow-Up*

While all efforts will be made to minimize attrition, subjects may withdraw from the study at any time, with or without reason and without prejudice to further treatment. Withdrawn subjects will not undergo any additional study follow-up, nor will they be replaced. All subjects enrolled in the clinical study (including those withdrawn from the clinical study or lost to follow-up) shall be accounted for and documented. When study subjects complete the study per the protocol requirements, their participation in the study is considered as complete, and they will be exited from the study.

If a subject withdraws from the clinical investigation, the reason(s) must be reported. If such withdrawal is due to problems related to device safety or performance, the investigator must ask for the subject's permission to follow his/her status/condition outside of the clinical study. This request needs to be documented in the subject file.

The sponsor may ask that withdrawn subjects are followed for information related to the safety of the device, if available.

Reasons for study exit will be captured in the EDC database and may include, physician discretion, subject choice to withdraw consent, lost to follow-up, or death. While study exit 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 must be completed at study exit (i.e., withdrawal, death, study completion) and an "End of Study" form must be completed. Subjects who are "lost-to-

follow-up" must have documented at least three attempts to contact them prior to completion of the "End of Study" form. Should the subject continue to be unreachable, he or she will be considered to have withdrawn from the study with the primary reason of lost to follow up. Data collected up to the point of subject withdrawal may be used for study analysis unless local regulations prohibit its use.

At the point of study completion and/or withdrawal, all adverse events must be assessed by the investigator. These events must be closed or documented as chronic. For those events that have been assessed as related to the device, these should be followed through resolution if possible and consent has been provided by the subject for data collection on these events.

10.4. *End of Study Action Plan*

At the conclusion of the study, patients receiving a device should be followed per standard of care practices at their site.

11. Study Methods

11.1. *Data Collection – Roll-In Subjects*

Roll-In subjects must meet all inclusion and none of the exclusion criteria and will not be randomized. For all Intent, Attempt, and Implant subjects (successfully received the WATCHMAN FLX Device) all visits are required, as defined in Table 11.2-1. However, Intent and Attempt subjects do not require LAA imaging at 3 and 12 months.
Study procedures and follow-up visits will occur as follows:

Table 11.1-1: Roll-In Study Visits

Visit	Timeframe
Consent	Must be performed within 40 days prior to implant
Pre-procedure LAA Imaging (TEE or CT)	- Optional for TEE guided WATCHMAN FLX implants - Required for ICE guided WATCHMAN FLX implants (must be performed after consent and prior to implant). These LAA imaging will be collected according to the Imaging Manual and submitted to the Core Lab for review
Implant	- Prior ablation (Sequential Group) – The WATCHMAN FLX implant procedure must be performed between 90 and 190 days of the most recent AF ablation procedure - Planned ablation (Concomitant Group) – The ablation and WATCHMAN FLX implant must be performed within 40 days of consent
3-Month Follow-up	90 ± 15 days from implant
12-Month Follow-up	365 ± 30 days from implant
24-Month Follow-up	730 ± 60 days from implant

Visit	Timeframe
36-Month Follow-up	1095 + 60 days from implant - this follow-up must occur on or after 1095 days and on or before 1155 days

11.2. *Data Collection – Randomized Subjects*

For all Intent, Attempt, and Implant subjects (successfully received the WATCHMAN FLX Device) all visits are required, as defined in Table 11.2-1. However, Intent and Attempt subjects do not require LAA imaging at 3 and 12 months.
Study procedures and follow-up visits will occur as follows:

Table 11.2-1: Randomized Subject Study Visits

Visit	Timeframe
Consent	Must be performed within 30 days prior to randomization
Randomization and Implant	- Prior ablation (Sequential group) – randomization must be performed between 90 and 180 days after the most recent AF ablation procedure. WATCHMAN FLX implant must be performed within 10 days following randomization - Planned ablation (Concomitant group) – the ablation +/- WATCHMAN FLX implant must be performed within 10 days of randomization
Pre-procedure LAA Imaging (TEE or CT)	- Optional for TEE guided WATCHMAN FLX implants - Required for ICE guided WATCHMAN FLX Implants (must be performed after randomization and prior to implant). These LAA imaging will be collected according to the Imaging Manual and submitted to the Core Lab for review
3-Month Follow-up	90 ± 15 days from randomization
12-Month Follow-up	365 ± 30 days from randomization
24-Month Follow-up	730 ± 60 days from randomization
36-Month Follow-up	1095 + 60 days from randomization - this follow-up must occur on or after 1095 days and on or before 1155 days

Note: Baseline data collection not available prior to consent must occur within 30 days prior to randomization. Study-specific procedures that are not standard of care must only be performed after the patient has signed informed consent.

Table 11.2-2: Data Collection Schedule

Procedure/Assessment	Baseline Assessment (Prior to Randomization)	Index Procedure (Ablation Procedure +/- WATCHMAN FLX)	Follow-up Visits*****			
			3-Month Follow-up	12-Month Follow-up	24-Month Follow-up	36-Month Follow-up
Informed consent process, including informed consent signature date	X	--	--	--	--	--
Demographics	X	--	--	--	--	--
Physical assessment	X	DG and CC	X	X	X	X
Medical history	X	--	--	--	--	--
Ablation Information	X	CC	O	O	O	O
Device information	--	DG	--	--	--	--
Procedure information and discharge assessment		DG and CC				
TTE	X***	--	--	--	--	--
Pre-procedure LAA imaging (TEE or CT)	--	DG^	--	--	--	--
Implant Procedure TEE/ICE	--	DG				
Follow-up LAA imaging (TEE or CT)	--	--	DG*	DG*	O	O
Brain Imaging (CT or MRI)	O**	O**	O**	O**	O**	O**
Serum Creatinine or GFR/eGFR	X	--	--	--	--	--
Platelet count and Hemoglobin level	X	--	--	--	--	--
NIH Stroke Scale	X	--	X	X	X	X
Modified Rankin Scale****	X	--	X	X	X	X
QoL (EQ-5D/SF12)	X	--	--	X	--	X
Medication Regimen Review	X	X	X	X	X	X
Adverse event assessment / device deficiency monitoring (as applicable)	X	X	X	X	X	X

X = All subjects; DG = Device Group; CC = Concomitant; O = Optional, data is collected if available
*Implant subjects only (does not include Intents or Attempts)
** For subjects with prior stroke or TIA, prior MRI/CT scans may be requested by BSC. For subjects who have a neurologic event during the trial, a copy of prior MRI/CT scans and MRI/CT scans from the event may be requested.
*** The baseline TTE will be done to evaluate all exclusion criteria to confirm subject eligibility Other recent cardiac imaging may be used to evaluate exclusion criteria if available in the subject's medical record. (see Section 11.10.1 for additional details).
^Pre-procedure LAA imaging (TEE or CT) is *required* for ICE guided WATCHMAN FLX implants and *optional* for TEE-guided WATCHMAN FLX implants.

**** Modified Rankin Scale may be completed via telehealth or phone at the discretion of a certified, trained study personnel.
***** Physical exam and NIH stroke scale may not be completed remotely if follow up visit is conducted via phone. QoL may be completed remotely if phone interview script is utilized.

11.3. *Study Candidate Screening*

Subjects selected for participation in this study may be from the investigator's general non-valvular atrial fibrillation population. Each investigator is responsible for selecting those who are appropriate for inclusion.

All subjects that sign the ICF will be entered in the EDC database. Subjects who sign the ICF but who are not randomized will be considered screen failure subjects and documented as such in the EDC database. Screen failure subjects should be exited immediately upon determining ineligibility.

11.4. *Informed Consent*

Subjects that have signed and dated the ICF are considered enrolled in the study. The informed consent process must be documented by the person obtaining consent and the documentation must be placed in the subject's file.

11.5. *Baseline Assessment Window*

Each subject has a maximum of 30 days to complete the baseline assessment following consent. The information below will be documented on case report forms for enrolled subjects:

- Demographics data including age at time of consent, sex, race, and ethnicity
- Medical, cardiac, and neurological history including: cardiovascular diseases; AF type (paroxysmal/persistent/long standing persistent) and time since AF diagnosis; prior history of ischemic stroke, hemorrhagic stroke and/or TIA; previous cardiac procedures; history of bleeding and location; NSAID use; risk factors, including those used to calculate HAS-BLED, and CHA_2DS_2-VASc
- Ablation information including ablation type, success, and rhythm post-ablation
- Physical assessment including vital signs, height, weight, and rhythm
- Current medication regimen review for the use of antiplatelet, anticoagulant, and antiarrhythmic medications
- Modified Rankin Scale (MRS) and NIH Stroke Scale (NIHSS)**
- Quality of Life Questionnaires (SF-12/EQ5D)**
- Serum Creatinine or Glomerular filtration rate (GFR/eGFR). Lab values may come from medical record if lab test was performed no greater than 210 days prior to randomization. Otherwise, lab values must be obtained during the baseline assessment window. Serum creatinine should be recorded if available. If serum creatinine is not available but eGFR is, eGFR should be recorded.
- Platelet count and Hemoglobin level. Lab values may come from medical record if lab test was performed no greater than 7 days prior to informed consent. Otherwise, lab values must be obtained during the baseline assessment window.

- Transthoracic Echocardiogram (TTE)*: For echo exclusion criteria assessment of EF, mitral stenosis, pericardial effusion, and PFO.

***Note:** The baseline TTE will be done to evaluate all exclusion criteria to confirm subject eligibility. Criteria obtained from a cardiac imaging performed within 180 days prior to randomization may be used if all the exclusion criteria can be evaluated. If all exclusion criteria were not obtained on the prior cardiac imaging, a TTE will have to be conducted at baseline. If a significant cardiac event occurs after the cardiac imaging which causes a change in cardiac status [i.e., major Congestive Heart Failure (CHF) decompensation] the baseline TTE must be repeated after informed consent and prior to randomization

**Note: The person administering the Quality-of-Life Questionnaires and stroke scales should be blinded to the subject's treatment assignment.

11.6. *Randomization*

Randomization will occur after all clinical and transthoracic echo criteria have been verified and the baseline assessment is complete. Randomization will occur no later than 30 days following consent. Subjects will be randomized 1:1 (Device : Control) and randomization will be stratified by sequential vs. concomitant planned ablation to help ensure balance of treatment assignments within the sequential and concomitant groups.

11.6.1. Sequential Ablation group

Randomization must occur between 90 and 180 days after the most recent AF ablation procedure. If the subject is randomized to the device group, implant must occur within 10 days of randomization.

For roll-in subjects, the implant must occur between 90 and 190 days after the most recent AF ablation.

11.6.2. Concomitant Ablation group

Randomization must occur within 10 days prior to the planned ablation. If the subject is randomized to the device group, catheter ablation and device implant must occur within 10 days of randomization.

11.7. *Index Procedure*

For all patients undergoing ablation and/or WATCHMAN FLX implantation, the following data will be collected:

- Physical assessment including vital signs, weight, and rhythm at time of the procedure

- Current medication regimen review for the use of antiplatelet, NSAID, anticoagulant, and antiarrhythmic medications
- Ablation information (patients undergoing Ablation) including ablation type, success, and rhythm post-ablation
- Adverse events experienced at index procedure and since enrollment. Refer to **Section 21** for detailed information on Safety reporting
- Discharge information (date, time)

For patients undergoing WATCHMAN FLX implantation, the procedure should be performed using standard of care methods established by the investigational site (e.g., sterile technique, personnel requirements, etc.). Implantation of the WATCHMAN FLX Device shall only be performed by study physicians trained in percutaneous and transseptal procedures who have completed the WATCHMAN and/or WATCHMAN FLX physician training programs. Refer to the WATCHMAN FLX Instructions for Use (IFU) for detailed instructions regarding the implantation and use of the WATCHMAN FLX Device.

Notes:

1. TEE is recommended for implant procedures; however, intracardiac echocardiography (ICE) is an acceptable alternative and may be used if the following conditions are met:
   - Pre-planning LAA imaging using TEE or CT must be completed prior to the implant procedure.
   - The implanting physician must have performed ≥ 25 WATCHMAN and/or WATCHMAN FLX procedures that involve the use of ICE.
   - If ICE is used, the site must perform pre-planning LAA imaging and must specify in the eCRF what imaging modality was used.

2. Do not proceed with the WATCHMAN FLX implant if the following is observed on TEE/ICE or fluoroscopy:
   - Intracardiac thrombus, LAA sludge (gelatinous, non-adherent, intracavitary echodensity more layered than dense spontaneous echo contrast (SEC) seen continuously throughout cardiac cycle) or dense SEC.
   - Complex atheroma with mobile plaque of the descending aorta and/or aortic arch.
   - The LAA anatomy will not accommodate a WATCHMAN FLX closure device.
   - High-risk PFO not detected at baseline.

Additional data collected for patients undergoing WATCHMAN FLX implantation:

- WATCHMAN FLX Device usage information, including device size and compression post-implant (Device Group only);
- Access System(s) usage information
- LAA imaging (as described in **Section 11.10**): LAA size/shape, number of lobes in LAA, and location of lobes to ostium;
- Device Release Criteria
- Name of implanting physician

- Duration of procedure and fluoroscopy
- Procedural medications
- Type of anesthesia
- Device Deficiencies
- Discharge information (date, time)

11.8. *Study Medication Regimen*

11.8.1. Device Group Study Medication Regimen

After the WATCHMAN FLX implant, Device Group subjects will be prescribed market-approved OAC and aspirin (75-100mg recommended) until the 3-month visit followed by aspirin until at least the 12-month visit (recommended for duration of the trial).

Any changes to protocol required medications or antiarrhythmic medications must be captured in the appropriate medication log.

11.8.2. Control Group Study Medication Regimen

Following randomization, control subjects must continue or start market approved OAC used per IFU for atrial fibrillation stroke prevention and should remain on it for the duration of the trial.

11.9. *Follow-Up Procedures (Office(preferred) or Phone call)*

Subjects will be followed at office visits (preferred) or phone visit at 3 months (90 ± 15 days from randomization), 12 months (365 ± 30 days from randomization), 24 months (730 ± 60 days from randomization), and 36 months (1095 + 60 days from randomization - visit must occur on or after day 1095).
Data from a physical assessment that is performed at an outside facility/non study trained personnel as part of the patient standard of care, may be utilized for the purpose of a protocol-required subject visit if completed within the follow up visit window. These data are to be reviewed by an investigator on the delegation log for inclusion of data as part of the study. Any other data that is collected from an outside facility as part of the standard of care (such as imaging) of the patient may be considered for inclusion as part of the study data.

Note: for Roll-in subjects the date of implant will be used to calculate Follow-up windows instead of the date of randomization.

The following will be assessed during each visit and documented on case report forms:

- Re-do ablations
- Documented atrial fibrillation episode since prior visit
- New onset atrial flutter or atrial tachycardia event (≥ 30 seconds in duration or from a 10 second 12-lead EKG; electrical and/or pharmacological cardioversion for AFL/AT)

- LAA imaging (as described in **Section 11.10**) for all Implant patients (submitted to core lab). LAA imaging data will include:
  - Device position
  - LAA seal status
  - Thrombus on the device surface (if visualized)
  - Intracardiac thrombus (if visualized)
  - Residual atrial septal shunt (if visualized)
- *Note – LAA imaging must be performed at 3-months and 12-months follow-up. If performed at the later visits or at the time of an adverse event, the information will be collected in the database. Intent and Attempt patients will not have 3-month or 12-month LAA imaging performed. Physical assessment including vital signs, weight, and rhythm at time of the visit.
- Modified Rankin Scale (MRS) and National Institutes of Health Stroke Scale (NIHSS). Note: NIHSS may not be performed remotely as part of a phone visit follow-up.
- Current medication regimen for the use of antiplatelet, NSAID, anticoagulant, and antiarrhythmic medications. Dose changes, medication interruptions, and medication cessation must be documented
- Quality of Life Questionnaires at 12-month and 36-months. Note: phone interview script will be available for use.
- Adverse events since previous visit. Refer to **Section 21** for detailed information on Safety reporting
- Device Deficiencies

11.10. *LAA Imaging (TEE, ICE, and CT)*

Roll-In and Device Group subjects may undergo pre-planning LAA imaging (typically TEE or CT) prior to WATCHMAN FLX Device implant. Pre-planning LAA imaging is not required for subjects undergoing TEE guided implants. If pre-planning imaging is performed, sites must note this on the data collection form and the imaging study should be saved and made available to the sponsor upon request. Pre-planning LAA imaging is required for subjects undergoing ICE guided implants and must be performed according to the imaging manual and sent to the Core Lab.

11.10.1. Baseline Transthoracic Echocardiogram (TTE)

The baseline TTE will be done to evaluate all exclusion criteria and to confirm subject eligibility. Criteria obtained from a cardiac imaging performed within 180 days prior to randomization may be used if all the exclusion criteria can be evaluated. If all exclusion criteria were not obtained on the prior cardiac imaging, a TTE will have to be conducted at baseline. If a significant cardiac event occurs after the cardiac imaging which causes a change in cardiac status [i.e., major Congestive Heart Failure (CHF) decompensation] the baseline TTE must be repeated after informed consent and prior to randomization.

If a subject meet any of the echo exclusion criteria, they should be screen failed and withdrawn immediately.

11.10.2. Implant and Follow-Up Imaging (TEE/ICE/CT)

All protocol required LAA imaging will be performed in accordance with the Core Lab Imaging Manual.

Implant LAA imaging (TEE recommended) will allow the investigator to obtain proper measurements of the LAA to correctly size the device, confirm device release criteria are met prior to device release, document absence of intracardiac thrombus, and confirm adverse events have not occurred during the implant procedure (i.e., pericardial effusion).

TEE is recommended for implant procedures; however, ICE may be used by investigators that meet the following conditions:

- Pre-planning with TEE or CT must be performed prior
- The implanting physician has performed ≥ 25 WATCHMAN and/or WATCHMAN FLX procedures that involve the use of ICE

The 3-month and 12-month LAA imaging (TEE recommended) is conducted to assess flow through and around the WATCHMAN FLX Device and to verify there is no device related thrombus (DRT) on the surface of the device. Adequate LAA seal is defined as demonstration of peri-device flow ≤5 mm around the margins of the WATCHMAN FLX Device.

Copies of all protocol required LAA imaging must be provided to the core lab per the Imaging Manual. LAA Imaging must be saved and available for review in the subject's medical or study file. Certain information from the LAA imaging conducted during the course of the study, including any non-protocol required LAA imaging (such as that performed in the context of an embolic event; see **Section 11.11.2**), will be captured on the study case report forms and submitted to the core lab. All study required images must be identified as defined in the Imaging Manual.

11.11. *Stroke or Systemic Embolism*

In the event that a subject experiences a stroke or systemic embolism (SE) during the course of the study, supporting documentation will be requested by the sponsor in an attempt to search for causes of stroke or embolic event.

11.11.1. Stroke Scales

The National Institutes of Health Stroke Scale (NIHSS) is an assessment tool which quantifies stroke-related neurological deficit. It must be conducted by neurologist or personnel who have a current certification to conduct the NIHSS. It is routinely collected at Baseline and all **office** Follow-up visits for all subjects and should be collected at the time of stroke or TIA event. If administered at the time of event, the NIHSS may be obtained by non-study personnel. The Modified Rankin Scale (MRS) score assesses the severity of stroke disability and functional dependence of all subjects. The assessment must be

performed by either a neurologist or personnel who have completed a certification for the MRS. The MRS to be collected at Baseline and Follow-up visits (office or phone) for all subjects. It must also be collected following the stroke or TIA event and at 90 (+/- 15) days after a stroke or TIA event. The MRS collected following the stroke or TIA event, and at 90 (+/- 15) days after a stroke or TIA event may be obtained by non-study personnel.

Note: The person administering the stroke scales should be blinded to the subject's treatment assignment.

Note: Neurologic consultation and cerebral vascular imaging should be performed if a subject's NIHSS and MRS have worsened and/or if there is suspicion of a neurologic event. If neurologic consultation and/or cerebral vascular imaging does occur, BSC may request a copy.

11.11.2. Stroke or Systemic Embolism and LAA Imaging (All subjects)

LAA imaging is strongly encouraged to help better ascertain the mechanism of the stroke or SE. This is not required, however if collected the imaging study should be saved and sent to the core lab per Imaging Manual. An optimal evaluation includes, where feasible based on subject status and technical considerations, evaluation of:

- LA thrombus – size, location, mobility, etc.
- Agitated saline contrast injection to evaluate presence of residual right to left shunt at the atrial level (persistence of PFO or residual puncture hole from transseptal catheterization for device placement)
- Presence, location, and grade of ascending and arch aortic atheroma
- Presence of worsening left ventricular dysfunction, "new" regional wall motion abnormality or presence of LV thrombus
- If applicable:
    - WATCHMAN FLX Device seal or presence (and measurement) of peri-device flow
    - WATCHMAN FLX Device thrombus or pannus – size, location, mobility, etc.

11.12. *Device Thrombus*

The most accurate determination of whether thrombus has formed on the surface of the WATCHMAN Device is through TEE evaluation. In the case of thrombus on the atrial facing side of the device, anticoagulation therapy should be initiated per hospital standard of care, for treatment of thrombus. After the course of anticoagulation therapy, a repeat imaging evaluation should be performed to confirm the thrombus has resolved. This is not required, however if collected the image should be saved and sent to the core lab per Imaging Manual. Cessation of anticoagulation after this timepoint is at the discretion of the investigator.

Any identification of device thrombus must be reported on an adverse event CRF. A copy of all imaging conducted for evaluation of potential thrombus must be sent to the Echo Core Lab and a copy must be maintained in the subject's records at the site.

TEE is recommended for follow-up imaging, but CT is an acceptable alternative. However, if findings suspicious for significant DRT (hypoattenuated thickening ≥ 3mm) or any pedunculated thrombus is noted on CT at follow-up, a TEE must be performed to determine if therapy is required.

11.13. *Device Seal*

For those subjects receiving a WATHCMAN FLX device, if adequate device seal (i.e., no leak > 5mm) is not obtained as demonstrated by the 3-month post-implant imaging (TEE or CT), the decision to continue or stop OAC and/or aspirin is at the discretion of the investigator and should be based on the individual subject's risk/benefit analysis (if possible, OAC should generally be prescribed). Follow-up imaging may be performed prior to the 12-month visit to reassess seal and inform the decision to stop OAC and/or aspirin. If device seal is not obtained as demonstrated by the interim or the 12-month imaging (TEE or CT), the decision to continue or stop OAC and/or aspirin is at the discretion of the investigator (if possible, OAC should generally be prescribed).

Note: Clinical study data establishing safety and effectiveness are based on demonstration of peri-device flow ≤5 mm as a measure of adequacy of LAA seal. Per the WATCHMAN FLX IFU, if adequate seal is not demonstrated, decision to discontinue OAC is at physician discretion provided that any leak demonstrated is ≤ 5 mm. Non-approved measures/procedures to improve seal (e.g. 'kissing' WATCHMAN, vascular plugs, endovascular coils, etc.) must not be attempted during the course of this study.

TEE is recommended for follow-up imaging, but CT is an acceptable alternative. However, if findings suspicious for significant peri-device leak (PDL) (e.g. leak width > 3mm) is noted on CT at follow-up, a TEE must be performed to determine if therapy is required.

11.14. *Study Completion*

All subjects will be followed through the completion of their 3-year follow-up visit, except for Screen Failure patients. An "End of Study" form will be completed to document the subject's study exit.

Once a study subject has exited the study, their participation in the study has ended. Appropriate eCRFs are completed indicating the status of the subject (i.e., end of study form). The table below provides information on the appropriate eCRFs to complete.

Table 11.14-1: Study Exit Data Collection Requirements

Type of Study Exit	Date to Use	Forms to complete
Subject withdrawal	Date of subject withdrawal	• End of Study form • Adverse Event (resolved/close any AEs or deem chronic)
Subject Lost to Follow-up	Date subject was last seen in office or last phone contact	• End of study • Adverse Event (resolve/close any AEs or deem chronic)
Subject Death	Date of Death	• Adverse Event (only one) with fatal outcome, resolve/close other AEs or deem chronic • End of Study Form
Complete all protocol visits	Date of last study visit	• End of Study Form • Adverse Event (resolve/close any AEs or deem chronic)
Screen Failure	Date the subject's ineligibility is determined	• "Screen Failure" designation on "Randomization" form within the "Baseline" folder • End of Study Form • Adverse Event (resolved/close any AEs or deem chronic)

11.15. *Source Documents*

The sponsor's representative, the monitor, will perform ongoing source data verification (SDV) against data transcribed to eCRFs. Source documents include, but are not limited to, hospital records, clinic/office charts, study specific worksheets, lab reports, subject questionnaires, etc. Source documents required to verify the validity and accuracy of eCRF data must never be obliterated or destroyed. To facilitate source document verification, the Investigator/Institution must provide Sponsor & monitor direct access to all source documents.

When clinical observations are entered directly into a site's EMR system, the electronic record can serve as the source document if the system has been validated in accordance with ICH requirements pertaining to computerized systems used in clinical research.
An acceptable computerized data collection system (for clinical research purposes) would be one that (1) allows data entry only by authorized individuals; (2) prevents the deletion or alteration of previously entered data and provides an audit trail for such data changes (e.g., modification of file); (3) protects the database from tampering; and (4) ensures data preservation. If a site's computerized medical record system is not adequately validated for the purposes of clinical research (as opposed to general clinical practice), applicable hardcopy source documents must be maintained to ensure that critical protocol data transcribed on the CRFs can be verified.

11.16. *Local Laboratory*

This study requires a local laboratory. Appropriate local laboratory certifications and documentation records are required to be maintained and filed at the site in the Investigative Site File through the enrollment period of the study.

12. Control Group Crossover

Subjects randomized to the Control Group that experience a primary efficacy endpoint event (stroke [including ischemic and/or hemorrhagic], systemic embolism) or primary safety event (ISTH major bleeding, or clinically relevant non-major bleeding) may be given the option of receiving a WATCHMAN FLX device prior to study completion. Crossing over without having experienced an endpoint event is discouraged. For those subjects that crossover, the Investigator should take into account the subject's individual risk/benefit profile when determining the timing of implantation after the primary endpoint event and associated medication.

Control Group subjects that receive any LAAC device will continue to be followed as Control Group subjects according to the intention-to-treat principle and their assigned subject visit windows. WATCHMAN FLX Implant information, including any procedure/device related events, as well as LAA imaging (recommended 3-month and 12-month LAA imaging from date of implant) will be collected and reported separately from the Device Group data analyses.

13. Statistical Considerations

The following sections provide an overview of the statistical considerations for the OPTION study. Further details can be found in the Statistical Analysis Plan.

13.1. *Endpoints*

13.1.1. Primary Efficacy Endpoint

The Primary Efficacy Endpoint is defined as the Kaplan Meier estimate of time to first occurrence of stroke (including ischemic and/or hemorrhagic), all cause death, and systemic embolism at 36 months.

13.1.1.1. Hypotheses

The objective of the Primary Effectiveness Endpoint analysis is to test the null hypothesis that the difference in cumulative incidence between the Device and Control groups is greater than a prespecified noninferiority margin δ. The null hypothesis will be tested vs. the one-sided alternative hypothesis that the difference in cumulative incidence is less than a noninferiority margin δ.

H_0: $S_1(t) \geq S_0(t) + \delta$

H_a: $S_1(t) < S_0(t) + \delta$,

Where $S_1(t)$ and $S_0(t)$ are the Kaplan Meier estimates for the cumulative incidence of stroke (including ischemic and/or hemorrhagic), all cause death, and systemic embolism at 36 months for the Device and Control groups, respectively.

13.1.1.2. Sample Size

The power and sample size were calculated employing Farrington Manning methods for non-inferiority using SAS version 9.4. The assumptions and parameters pertaining to this design are as follows:

- Power = 85.9%
- Alpha = 0.025 (one-sided)
- Expected Device and Control group performance: cumulative incidence rate of 10% at 36 months in both groups
- A noninferiority margin $\delta = 5\%$
- Attrition: cumulative attrition rate of 15% in the Device Group and in the Control group at 36 months.

The expected cumulative incidence of 10% at 36 months in the Device group was derived from historical event rates from the PROTECT AF, CAP, PREVAIL, and CAP2 studies. WATCHMAN subjects with previous ablations from these studies experienced a 14.4% event at 3 years. The cumulative incidence is expected to be lower in the OPTION study due to enhanced implant experience over time, device improvements, and a decreased baseline risk profile for subjects enrolled in the OPTION study. The expected cumulative incidence in the Control arm is expected to be equal to that of the Device arm.

The non-inferiority margin of 5% represents a relative risk of 1.5.

Given the above assumptions, 1360 subjects will be required. In order to account for up to 15% expected rate of attrition which includes subjects randomized but not treated and subjects withdrawn or lost-to-follow-up through 36 months, a total of 1600 (1360/(1-0.15)) subjects need to be enrolled.

A sample size of 1600 subjects provides 85.9% power for the Primary Effectiveness Endpoint analysis. Therefore, a maximum sample size of 1600 is determined.

13.1.1.3. Statistical Methods

The primary efficacy endpoint event rate from the WATCHMAN FLX Device and Control arms, $S_1(t)$ and $S_0(t)$, respectively, will be estimated by the Kaplan Meier method. The time point of 36 months is defined as the 1095^{th} day post-randomization. The 97.5% one-sided upper bound of confidence limit of the difference between WATCHMAN FLX and Control rates will be calculated using Greenwood formula for the variance of the Kaplan Meier estimates. The objective is met if this confidence limit is less than the predefined noninferiority margin of 5%.

If the non-inferiority hypothesis objective is met, a superiority test will be subsequently performed and a one-sided p-value of 0.025 will be considered significant.

13.1.2. Primary Safety Endpoint

The Primary Safety Endpoint is Kaplan Meier estimate of time to first occurrence of non-procedural bleeding (ISTH major bleeding and clinically relevant non-major bleeding) through 36 months. Non-procedural events are those occurring after 3 days.

13.1.2.1. Hypotheses

The objective of the Primary Safety Endpoint analysis is to test the null hypothesis that time-to-event distributions do not differ between the Device and Control groups. The null hypothesis will be tested vs. the 2-sided alternative hypothesis that the time-to-event curves are different.

H_0: $S_1(t) = S_0(t)$
H_a: $S_1(t) \neq S_0(t)$,

Where $S_1(t)$ and $S_0(t)$ are the time-to-event curves for ISTH major bleeding and clinically relevant non-major bleeding of the Device and Control groups, respectively.

13.1.2.2. Sample Size

This sample size was calculated employing log rank test methodology using EAST 6 software with the following assumptions:

- Expected event rate of the Device group= 14% and of the Control group = 20%
- 2-sided alpha = 5%
- Power = 86.4%
- Expected attrition rate = 20%
- Required sample size = 1600 subjects

The expected Primary Safety Endpoint event rate in the Device group is based off the combined PROTECT AF, CAP, PREVAIL, and CAP2 WATCHMAN arms. The observed rate of non-procedural major bleeding at 36 months in these subjects was 9.4%. The Primary Safety Endpoint event rate in the OPTION Device group is then expected to be 14%, which accounts for similar non-procedural major bleeding risk as in previous WATCHMAN studies but with the addition of clinically relevant non-major bleeds unrelated to the implant procedure. The expected rate of 20% in the Control group is based off the rates of major or clinically relevant non-major bleeds reported in the ARISTOTLE, ENGAGE, and ROCKET-AF studies.

In order to account for up to 20% expected rate of attrition which includes subjects who die, withdraw, or are lost-to-follow-up through 36 months without experiencing an endpoint event, a total of 1600 (1280/(1-0.2)) subjects need to be enrolled. A sample size of 1600 subjects provides approximately 86.4% power for the Primary Safety Endpoint analysis.

13.1.2.3. Statistical Methods

All subjects in the randomized cohort will be included in the analysis. Log- rank test will be performed including all subjects in database at the time of analysis post 36 months. The objective is met if p-value of the log-rank test is less than 0.05.

13.1.3. Secondary Endpoint

The Secondary Endpoint is the Kaplan Meier estimate of time to first occurrence of all ISTH major bleeding at 36 months.

13.1.3.1. Hypotheses

The objective of the Secondary Endpoint analysis is to test the null hypothesis that for the difference in cumulative incidence between the Device and Control groups is greater than a prespecified noninferiority margin δ. The null hypothesis will be tested vs. the one-sided alternative hypothesis that the difference in cumulative incidence is less than a noninferiority margin δ.

H_0: $S_1(t) \geq S_0(t) + \delta$

H_a: $S_1(t) < S_0(t) + \delta$,

Where $S_1(t)$ and $S_0(t)$ are the Kaplan Meier estimates for cumulative incidence of all ISTH major bleeding at 36 months for the Device and Control groups, respectively.

13.1.3.2. Sample Size

The power and sample size were calculated employing Farrington Manning methods for non-inferiority using SAS version 9.4. The assumptions and parameters pertaining to this design are as follows:

- Power = 84.3%
- Alpha = 0.025 (one-sided)
- Expected Device and Control group performance: cumulative incidence of 11% at 36 months in both groups
- A noninferiority margin δ = 5.25%
- Attrition: cumulative attrition rate of 20% in the Device Group and in the Control Group at 36 months.

The expected device time-to-event rate of 11% at 36 months was derived from subjects with previous ablations from the combined PROTECT AF, CAP, PREVAIL, and CAP2 WATCHMAN arms. The observed event rate in these subjects was 13.6% event at 3 years. This rate is expected to be lower in the OPTION device arm due to enhanced implant experience over time, device improvements, and the use of DOACs post-implant rather than Warfarin. The expected event rate in the Control group is expected to be similar to that of the Device group. The non-inferiority margin of 5.25% represents a relative risk of 1.48.

Given the above assumptions, 1280 subjects will be required. In order to account for up to 20% expected rate of attrition which includes subjects who die, withdraw or are lost-to-follow-up through 36 months without experiencing an endpoint event, a total of 1600 (1280/(1-0.2)) subjects need to be enrolled.

A sample size of 1600 subjects provides approximately 84% power for the Secondary Endpoint analysis.

13.1.3.3. Statistical Methods

All subjects in the randomized cohort will be included in the analysis. The secondary endpoint event from the Watchman device and control arms, $S_1(t)$ and $S_0(t)$ at 36 months, defined as the 1095^{th} day post-randomization, will be estimated by the Kaplan Meier method. The 97.5% one-sided upper bound of confidence limit of the difference between WATCHMAN FLX and Control rates at 36 months will be calculated using Greenwood formula for the variance of the Kaplan Meier estimates. The objective is met if this confidence limit is less than the predefined noninferiority margin of 5.25%.

If the non-inferiority hypothesis objective is met, a superiority test will be subsequently performed and a one-sided p-value of 0.025 will be considered significant.

13.2. *General Statistical Methods*

13.2.1. Analysis Sets

The primary analysis for each of the Primary and Secondary Endpoints will be performed on an intent-to-treat basis, with each subject analyzed as being part of their randomized group regardless of the actual treatment received. Additional analysis sets per actual treatment received will be performed for the Primary and Secondary Endpoints as sensitivity analyses.

13.2.2. Control of Systematic Error/Bias

Selection of subjects for enrollment will be made from the Investigator's usual subject load. All subjects meeting the eligibility criteria and having signed the ICF will be eligible for enrollment in the study. To control for the potential bias that could be introduced via sponsor classification of adverse events, a Clinical Events Committee (CEC) will adjudicate all major events to be used in the data analyses.

13.2.3. Number of Subjects per Investigative Site

To avoid any site effect and bias, no site will be authorized to implant or attempt more than 15% of the 1600 randomized subjects (n = 240) per this protocol without prior approval from the sponsor.

13.3. *Data Analyses*

13.3.1. Description of Baseline Variables

Baseline demographic and clinical variables will be summarized for each of the treatment groups for both the intent-to-treat and per protocol populations. All continuous variables will be summarized as means, medians, standard deviations and interquartile ranges and compared between treatment groups using one-way analysis of variance (ANOVA) or the non-parametric Kruskal-Wallis test. Categorical variables will be summarized as frequencies and percentages and compared between treatment groups using Pearson's χ^2 test or Fisher's exact test, as appropriate. Ordinal variables will be compared using Cochran-Mantel-Haenszel test with row mean scores.

A by-subject listing of key demographic data and baseline characteristics, including variables used for stratification will be presented.

13.3.2. Additional Endpoints/Measurements

1. The occurrence and incidence of:
    - Stroke
        - Ischemic stroke
        - Hemorrhagic stroke
        - Disabling stroke
        - Non-disabling stroke
    - Systemic embolism
    - Procedural and non-procedural bleeding and classifications (i.e., major bleeding per ISTH; and clinically relevant non-major bleeding)
    - All-cause death
    - Cardiovascular/unknown death
    - Non-cardiovascular death
    - Device related Thrombus
2. Procedural success
3. Rates of effective (defined as jet size of ≤5mm) and complete (defined as no peri-device flow) LAA closure at 3- and 12-months post implant
4. Freedom from AF

Clinical recurrences of atrial fibrillation are defined as any of the following:

- Documented atrial fibrillation episode, or new onset of atrial flutter or atrial tachycardia event (≥ 30 seconds in duration or from a 10 second 12-lead EKG) post-randomization or index procedure, whichever is later and the end of study.
- Any of the following interventions for atrial fibrillation, or new onset of atrial flutter or atrial tachycardia post-randomization or index procedure, whichever is later and the end of study:
    - Repeat ablation procedure

  - Electrical and/or pharmacological cardioversion for AF/AFL/AT
- Prescribed a higher dose of any AAD for atrial arrhythmias documented at baseline
- Prescribed a new AAD for atrial arrhythmias not documented at baseline
- Failure to discontinue AAD between 91 days and end of study post ablation procedure

5. Healthcare resource utilization
6. Quality of life

13.3.3. Subgroup Analyses

Per study design, the following subgroups will be analyzed for the Primary Endpoints within the study:

- Sequential vs. Concomitant
- Sex (Female vs. Male)
- Age at time of consent (< 75 years vs. ≥ 75 years)
- Stroke risk (CHA_2DS_2-VASc Score)
- Bleeding risk (HAS-BLED Score)
- AF type

Time-to-event curves will be constructed for each treatment group, HRs and log rank test p-values will be calculated within each subgroup, and subgroup by treatment interactions will be tested using Cox regression. P-values will be provided without multiplicity adjustments.

In addition, health care utilization will be compared between Concomitant and Sequential groups.

13.3.4. Justification of Pooling

Poolability will be assessed across site, geographical region, and sequential vs. concomitant ablation for each primary endpoint. Results will also be presented separately for site, geographical region, and sequential vs. concomitant ablations regardless of the results of the poolability assessments. Sites that successfully implanted with 5 subjects or fewer will be considered "small sites" and will be grouped together as one site per geographical region for the purpose of poolability assessment.

13.3.4.1. Pooling of Investigational Centers

Center-to-center heterogeneity will be assessed for the Primary and Secondary endpoints using a shared frailty model. Time to event variables will be modelled on randomized treatment group, with investigational center included as a random effect with a lognormal distribution. Centers will be deemed heterogeneous with respect to the Primary Effectiveness Endpoint if the p-value from Wald test for the investigational center random effect is <0.15.

13.3.5. Multivariable Analyses

Multivariable analysis, such as COX regression analysis with covariate adjustment, will be performed in light of evidence that randomization did not result in balance treatment groups, according to baseline $CHADS_2$ or CHA_2DS_2-VASc scores. These analyses will be performed as ancillary to the primary endpoint analyses.

13.3.6. Sensitivity Analyses for the Primary Endpoints

Per Kaplan-Meier method, subjects who count towards attrition will still contribute towards the primary effectiveness endpoint event rates until the time at which they are lost to follow-up (i.e., censored). Sensitivity analyses will be performed according to the following:

Regarding attrition bias, baseline characteristics will be compared across attrition vs non-attrition subjects for each primary endpoint to determine if subjects counted towards attrition had a higher baseline risk profile. In addition, tipping-point analysis will be conducted to determine the lowest/highest assumed rate in attrition subjects (assuming they had been followed for 3-years) such that the alternative hypothesis is no longer met/failed. The probability of observing this tipping-point rate in the attrition subjects (assuming a true rate equal to that observed in non-attrition subjects) will then be calculated to determine the likelihood of observing this tipping-point rate in the attrition subjects.

13.3.7. Missing Data

Every effort will be undertaken to minimize missing data. In time-to-event outcomes drop-outs will be censored at the time of last follow-up, consistent with the Kaplan-Meier methodology. The last follow-up date will be the latest of the following dates for each subject: date of adverse event, randomization date, implant procedure date, discharge date, and follow-up visit date. Unless otherwise specified, no statistical techniques will be used to impute missing data for continuous or categorical outcomes. The number of subjects included in each analysis will be reported so that the reviewer can assess the potential impact of missing data.

For each primary and secondary endpoint, a sensitivity analysis will be conducted to assess the impact of censored data and will include a worst-case analysis.

13.3.8. Other Analyses

Quality of Life

Clinical trials increasingly recognize the value of including patient reported outcome measures in their design. To understand the impact of atrial fibrillation related procedures and disease management on patient's quality of life, the quality-of-life instruments used for the trial will be the EQ-5D-5L and the 12-Item Short Form Health Survey (SF-12) for generic instruments. The EQ-5D 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 SF-12 includes 12 dimensions with varying levels of response. Subjects will be asked to complete the questionnaires at the enrollment visit as well as at the 12- and 36-month follow-up visit.

Other data analyses and results not enumerated in the protocol will be described in the Statistical Analysis Plan.

13.3.9. Interim Analyses

No formal interim analyses are planned for the purpose of stopping this study early for declaring effectiveness or for futility.

13.3.10. 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.

14. Health Economics Outcomes

A formal health economics analysis may be completed as part of this trial study, given meaningful clinical results are obtained. This will take into consideration any differences in survival, complication rates, quality of life, and resource utilization. The EQ-5D and SF-12 may be used to assess health utilities. We will capture health care utilization measures at all sites. These inputs may be used in health economics analysis performed.

15. Data Management

15.1. *Data Collection, Processing, and Review*

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

The clinical database will reside on a production server hosted by iMedidata 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.

15.2. *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.

15.3. *Core Laboratories*

An independent core laboratory will be utilized to review LAA imaging collected at protocol required time points during the study. All interpretations of LAA imaging for purposes of subject care will be conducted by each site's investigator and/or Echocardiographer. The Core Lab will not be utilized as a means of reference for subject management decisions.

LAA imaging from pre-planning images for ICE guided implants, implant, 3-months, and 12-months will be collected by each study site according to the Imaging Manual and submitted to the Core Lab for review. The Core Lab will provide the sponsor with summary of results for reporting purposes.

16. Deviations

An Investigator must not make any changes or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency. An investigator shall notify the sponsor and the reviewing IRB/EC/REB and the regulatory authority if applicable of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency, and those deviations which affect the scientific integrity of the clinical investigation. Such notice shall be given as soon as possible, but no later than 5 working days after the emergency occurred, or per prevailing local requirements, if sooner than 5 working days.

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

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

17. Device/Equipment Accountability

17.1. *Commercial Equipment*

The commercially approved WATCHMAN Access System may be used in all geographies. The WATCHMAN TruSeal Access System will be used in all geographies in which it is commercially approved. When possible, the WATCHMAN TruSeal Access System should be used. Investigators should have experience using the WATCHMAN FLX Device and/or TruSeal Access System, prior to utilizing them together in the trial.

In geographies where the CE mark applies, and other applicable geographies, the commercial WATCHMAN FLX Device and Delivery system will be utilized under the OPTION commercial directions for use with the additional requirement of a 12-month LAA imaging examination. This aligns with the OPTION IFU which is used in geographies where the CE mark does not apply.

If additional WATCHMAN Access Systems generation(s) become commercially available during the enrollment phase of the study, these Access Systems may be used in OPTION.

17.2. *Investigational Equipment*

In geographies where WATCHMAN FLX may not be commercially available, the WATCHMAN FLX Device and Delivery System is labeled as investigational and will be utilized under the same OPTION investigational directions for use.

The investigational devices/equipment shall be securely maintained, controlled, and used only in this clinical study. The sponsor shall keep records to document the physical location of all investigational devices/ equipment from shipment of investigational devices from BSC or designated facility/equipment to the investigation sites until return or disposal. Equipment shall be returned in the condition in which it was provided, reasonable wear and tear excepted.

Records shall be kept by investigational site to document the physical location and conditions of storage of all investigational devices/equipment.
The principal investigator or an authorized designee shall keep records documenting the receipt, use, return and disposal of the investigational devices/equipment, which shall include the following:

- Date of receipt
- Identification of each investigational device/piece of equipment (batch number or unique code)
- Expiry date, as applicable
- Date or dates of use
- Subject identification
- Date on which the investigational device/piece of equipment was returned/explanted from subject, if applicable
- Date of return (and number) of unused, expired, or malfunctioning investigational devices/equipment, if applicable.

18. Compliance

18.1. *Statement of Compliance*

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

This study will be conducted in accordance with 21 CFR part 56, part 50, part 54 and part 812, EN ISO 14155 Clinical Investigation of Medical Devices for Human Subjects, relevant parts of the ICH Guidelines for Good Clinical Practice, ethical principles that have their origins in the Declaration of Helsinki, and applicable individual country laws and regulations. The study shall not begin until the required approval/favorable opinion from the IRB/EC/REB and/or regulatory authority has been obtained, if appropriate. Also, the study shall not begin prior to issuance of the site Authorization to Enroll, as provided by the sponsor. Any additional requirements imposed by the IRB/EC/REB or regulatory authority shall be followed, if appropriate.

18.2. *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, ISO 14155, ethical principles that have their origins in the Declaration of Helsinki, any conditions of approval imposed by the reviewing IRB/EC/REB, and prevailing local and/or country laws and/or regulations, whichever affords the greater protection to the subject.

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

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

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

All investigators will provide their qualifications and experience to assume responsibility for their delegated tasks through up-to-date curriculum vitae or other relevant documentation and disclose potential conflicts of interest, including financial, that may interfere with the conduct of the clinical study or interpretation of results.

18.2.1. Delegation of Responsibility

When specific tasks are delegated by an investigator, including but not limited to conducting the informed consent process, the Principal Investigator is responsible for providing

appropriate training, 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 investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

18.3. *Institutional Review Board/ Ethics Committee*

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

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

Any amendment to the protocol will require review and approval by the IRB/EC/REB before the changes are implemented to the study. All changes to the ICF will be IRB/EC/REB approved; a determination will be made regarding whether a new ICF needs to be obtained from participants who provided consent, using a previously approved ICF. Annual IRB/EC/REB approval and renewals will be obtained throughout the duration of the study as required by applicable local/country laws or regulations or IRB/EC/REB requirements. Copies of the study reports and the IRB/EC/REB continuance of approval must be provided to the sponsor.

18.4. *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.

18.4.1. 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 implant, 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 devices.

At the request of the investigator and while under investigator supervision, BSC personnel may assist with the conduct of testing specified in the protocol and may perform certain activities to ensure study quality.
Typical tasks may include the following:

- Providing technical expertise/support during implant procedures and/or LAA imaging evaluations in conjunction with the principal investigator or their delegated site staff
- 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

18.5. *Insurance*

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

19. 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.

20. Potential Risks and Benefits

20.1. *Anticipated Adverse Events*

Potential procedural risks associated with the WATCHMAN FLX implant procedure and a cardiac ablation are similar to those encountered in other interventional cardiac procedures requiring trans-septal puncture and intracardiac catheter manipulation and cardiac catheterization procedures. These are included in the table below.

Table 20.1-1: Anticipated Adverse Events

• Air embolism • Airway trauma • Allergic reaction to the contrast media, anesthetic, WATCHMAN Implant material, or medication • Altered mental status • Anemia requiring transfusion • Anesthesia risks • Angina • Anoxic encephalopathy • Arrhythmias • Atrial septal defect • Bruising, hematoma or seroma near the catheter insertion site • Cardiac perforation • Chest pain/discomfort • Confusion post procedure • Congestive heart failure • Contrast related nephropathy • Cranial bleed • Death • Decreased hemoglobin • Deep vein thrombosis • Device embolism • Device fracture • Device thrombosis • Edema • Embolism • Excessive bleeding • Fever	• Hypotension • Hypoxia • Improper wound healing • Inability to reposition, recapture, or retrieve the device • Infection / pneumonia • Interatrial septum thrombus • Intratracheal bleeding • Major bleeding requiring transfusion • Misplacement of the device / improper seal of the appendage / movement of device from appendage wall • Myocardial erosion • Nausea • Oral bleeding • Pericardial effusion / tamponade • Pleural effusion • Prolonged bleeding from a laceration • Pseudoaneurysm • Pulmonary edema • Renal failure • Respiratory insufficiency / failure • Stroke – Ischemic • Stroke – Hemorrhagic • Surgical removal of the device • Systemic embolism • TEE complications (e.g., throat pain, bleeding, esophageal trauma) • Thrombocytopenia • Thrombosis

• Fistula • Groin pain • Groin puncture bleed • Hematuria • Hemoptysis	• Transient ischemic attack (TIA) • Valvular or vascular damage • Vasovagal reactions

20.2. *Anticipated Adverse Device Effects*

From the Anticipated Adverse Events listed above, the following anticipated adverse device effects (ADE) have been identified for the WATCHMAN FLX Device and are as follows:

- Additional surgery if the device is not placed in the correct position
- Allergic reaction to the implant materials
- Device misplacement
- Device embolization/migration
- Device fracture or extrusion
- Excessive bleeding
- Hypertrophic scarring or thrombosed veins
- Device thrombosis
- Inability to move or retrieve device
- Inability to implant the device

20.3. *Risks Associated with the Study Device*

An overview of anticipated adverse (device) effects and risks associated with the WATCHMAN FLX device is included in the both the commercial and the study Instructions for Use (IFU).

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

Subjects who receive the WATCHMAN FLX Device may stop anticoagulation therapy as early as the 3-months follow-up visit if they meet anticoagulation cessation guidelines; therefore, at that time, subjects may be at an increased risk of stroke. Anticoagulation is the most frequently utilized modality for reducing the risk of stroke in atrial fibrillation. The WATCHMAN FLX Device is designed to be used instead of long-term anticoagulation. The absence of an anticoagulant may represent a risk, especially if the device is not effective in preventing stroke.

For subjects in the concomitant group (i.e., who will undergo ablation +/- WATCHMAN implantation), risks associated with the ablation procedure should be discussed with the physician. Additionally, it is currently not known whether subjects in the concomitant group may be at increased risk for device embolization or other adverse events due to the combined

ablation and WATCHMAN FLX implant. It is expected that the risks associated with the concomitant procedure are similar to the risk of when each procedure is performed separately.

20.5. *Medication Risks*

Risks associated with OAC or antiplatelet usage should be referenced in each medication's IFU and may include the following:

- Increased bruising
- Increased bleeding tendencies
- Gastrointestinal (GI) side effects including stomach pain, heartburn, nausea, vomiting and gross GI bleeding
- Elevated hepatic enzymes, blood urea nitrogen and serum creatinine, hyperkalemia, proteinuria, and prolonged bleeding time
- Thrombotic thrombocytopenic purpura (TTP)
- Thrombocytopenia

20.6. *Risk Minimization Actions*

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

20.7. *Anticipated Benefits*

WATCHMAN FLX is designed to enhance the user experience and acute safety profile for the WATCHMAN LAA Closure Technology compared to the WATCHMAN LAAC Device (also called WATCHMAN Gen 2.5). The potential benefit of implanting the WATCHMAN FLX Device is its expected ability to prevent thromboembolic events originating in the LAA. The WATCHMAN FLX Device may protect against ischemic stroke and systemic thromboembolism. In subjects implanted with the device, the elimination of long-term anticoagulation therapy may reduce bleeding complications associated with long-term anticoagulation, such as hemorrhagic stroke or gastrointestinal major bleeding events.

20.8. *Risk to Benefit Rationale*

Risk management activities, including Hazard Analyses (HA) and Failure Mode Effects Analyses (FMEA), have been performed on the WATCHMAN FLX Device to identify and analyze known and foreseeable hazards 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.

In addition, investigational teams selected to conduct the study will be experienced and skilled in interventional cardiology and/or electrophysiology with transseptal and left heart experience, will have completed the WATCHMAN FLX Physician Training program and will have access to modern high technology medical facilities to conduct those procedures.

21. Safety Reporting

21.1. *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 from time of enrollment through 3-year follow-up including any of following categories:

- Unanticipated Adverse Device Effects/Unanticipated Serious Adverse Device Effects
- Serious Adverse Events regardless of cause - Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without serious deterioration in health, is not considered a serious adverse event.

In addition, the following events must also be reported:

- WATCHMAN FLX Device and/or WATCHMAN FLX index procedure related adverse events
- Adverse events related to protocol required testing (i.e., TEE or other LAA imaging)
- Adverse events where systemic embolism is suspected and/or confirmed, regardless of relationship to the WATCHMAN FLX Device.
- Adverse events related to WATCHMAN FLX Device (device thrombus, embolization, erosion, etc.).
- Adverse events related to the ablation procedure (if the procedure occurred after consent)
- Adverse events related to protocol required OAC or antiplatelet therapy
- All bleeding events regardless of relationship to the WATCHMAN FLX Device.
- All strokes (regardless of cause) and transient ischemic (TIA) regardless of relationship to the WATCHMAN FLX Device.
- New findings/updates in relation to already reported 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 index procedure, it should be submitted as an adverse event and/or device deficiency.

Any reportable event experienced by the study subject after informed consent and once considered enrolled in the study (as defined in study subject classification section) must be recorded in the eCRF.

Underlying diseases 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 21.2-1 for AE definitions).

Atrial fibrillation recurrence is not considered an AE unless there is a worsening of the condition as determined by the investigator. If an additional ablation procedure is required by any subject, the procedure should be reported in the AE eCRF whenever it meets the criteria for a serious adverse event or represents a worsening condition. The ablation should be reported as a corrective action for the subject condition.

Refer to Section 20 for the known risks associated with the study device(s).

21.2. *Definitions and Classification*

Adverse event definitions are provided in Table 21.2-1. Administrative edits were made on the safety definitions from applicable regulations and guidance including (but not limited to) 21 CFR Part 815, ISO 14155 and EU MDR 2017/745/MDCG 2020-10/1 Guidance on Safety Reporting in Clinical Investigations for clarification purposes.

Table 21.2-1: 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 investigational medical device and whether anticipated or unanticipated. **NOTE 1**: This includes events related to the investigational medical device or comparator. **NOTE 2**: This definition includes events related to the procedures involved. **NOTE 3**: For users or other persons, this definition is restricted to events related to the investigational medical device.
Adverse Device Effect (ADE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	Adverse event related to the use of an investigational medical device **NOTE 1**: This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.

Table 21.2-1: Safety Definitions

Term	Definition
	NOTE 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device. **NOTE 3**: This includes 'comparator' if the comparator is a medical device.
Serious Adverse Event (SAE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	Adverse event that led to any of 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) Led to fetal distress, fetal death, or a congenital abnormality or birth defect including physical or mental impairment. **NOTE 1:** Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without a serious deterioration in health, is not considered a serious adverse event.
Serious Adverse Device Effect (SADE) *Ref: ISO 14155* *Ref: 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.
Serious Health Threat	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

Table 21.2-1: Safety Definitions

Term	Definition
Ref: ISO 14155	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. **NOTE 2**: This definition includes device deficiencies related to the investigational medical device or the comparator.
The following definitions will be used for defining hospitalization or prolongation of hospitalization for SAE classification purposes:	
Hospitalizations	Hospitalization does not include: • emergency room visit that does not result in in-patient admission Note: although an emergency room visit does not itself meet the definition for hospitalization, it may meet other serious criteria (e.g., medical or surgical intervention to prevent permanent impairment or damage) • elective and pre-planned treatment/surgery for a pre-existing condition that is documented in the subject's record at the time of consent/enrollment • admission for social reasons and/or respite care in the absence of any deterioration in the subject's general condition (e.g., subject is homeless, caregiver relief) • pre-planned, protocol-specified admission related to the clinical study (e.g., procedure required by protocol)
Prolongation of hospitalization	In-patient admission to the hospital that is prolonged beyond the expected standard duration for the condition under treatment. Note: new adverse events occurring during the hospitalization are evaluated to determine if they prolonged hospitalization or meet another SAE criteria.

21.3. *Relationship to Study Device(s)*

The Investigator must assess the relationship of the reportable AE to the study device and/or index procedure. See criteria in **Table 21.3-1:**

Table 21.3-1: Criteria for Assessing Relationship of Study Device, Comparator, 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 is not a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has no temporal relationship with the use of the investigational device or the procedures; - the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; - the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event; - the event involves a body-site or an organ not expected to be affected by the device or procedure; - the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors); - the event does not depend on a false result given by the investigational device used for diagnosis, when applicable; harms to the subject are not clearly due to use error; - In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.
Unlikely Related *Ref: MDCG 2020-10/1*	The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
Possibly Related *Ref: 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, comparator, or the relationship with procedures seems relevant and/or the event cannot be reasonably explained by another cause, but additional information may be obtained.

Table 21.3-1: Criteria for Assessing Relationship of Study Device, Comparator, Procedure to Adverse Event

Classification	Description
Causal Relationship *Ref: MDCG 2020-10/1*	The serious event is associated with the study device or 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 investigational device use/application or procedures; - the event involves a body-site or organ that -the investigational device or procedures are applied to; -the investigational device or procedures have an effect on; - the serious event follows a known response pattern to the medical device (if the response pattern is previously known); - the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible); - other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; - harm to the subject is due to error in use; - the event depends on a false result given by the investigational device used for diagnosis, when applicable; - In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

21.4. *Investigator Reporting Requirements*

The communication requirements for reporting to BSC are as shown in Table 21.4-1.

Table 21.4-1: Investigator Reporting Requirements

Event Classification	Communication Method	Communication Timeline (21 CFR Part 812, *MDCG 2020-10/1*)
Serious Health Threat	Complete applicable eCRF/paper form 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.

Table 21.4-1: Investigator Reporting Requirements

Event Classification	**Communication Method**	**Communication Timeline** (21 CFR Part 812, *MDCG 2020-10/1*)
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.	• Immediately, but no later than 3 calendar days of first becoming aware of the event or as per local/regional regulations. • Reporting required through the end of the study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• Upon request of sponsor
Serious Adverse Device Effects	Complete AE eCRF page with all available new and updated information.	• Immediately but no later than 3 calendar days of first becoming aware of the event or as per local/regional regulations. • Reporting required through the end of the study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• When documentation is available • Upon request of sponsor
Device Deficiencies (including but not limited to, malfunctions, use errors and inadequacy in information supplied by the manufacturer, including labeling) 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 Device Deficiency eCRF with all available new and updated information.	• Immediately but no later than 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

Table 21.4-1: Investigator Reporting Requirements

Event Classification	**Communication Method**	**Communication Timeline** (21 CFR Part 812, *MDCG 2020-10/1*)
Reportable Adverse Event (see section 21) including Adverse Device Effects	Complete AE eCRF page, which contains such information as date of AE, treatment of AE resolution, assessment of seriousness and relationship to the device.	• In a timely manner (e.g., Recommend within 10 business days) after becoming aware of the information • Reporting required through the end of the study
	Provide all relevant source documentation (de-identified/pseudonymized) for reported event, as requested by sponsor.	• Upon request of sponsor

21.5. *Boston Scientific Device Deficiencies*

Device deficiencies for study devices (WATCHMAN FLX Delivery System, consisting of a delivery catheter and pre-loaded closure device) will be documented and reported to BSC on the Device Deficiency eCRF. If possible, the device(s) should be returned to BSC for analysis. Instructions for returning the device(s) will be provided on an individual basis. 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.

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

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

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

21.7. *Subject Death Reporting*

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

22. Informed Consent

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

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

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

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

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

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

Failure to obtain subject consent will be reported by BSC to the applicable regulatory authority according to their requirements (e.g., FDA requirement is within 5 working days of learning of such an event). Any violations of the informed consent process must be reported as deviations to the sponsor and local regulatory authorities (e.g., IRB/EC/REB), as appropriate.

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

23. Committees

23.1. *Safety Monitoring Process*

To promote early detection of safety issues, the Clinical Events Committee and Data Monitoring Committee will provide evaluations of safety events. Success of this program requires dynamic collection of unmonitored data as soon as the event is reported. During regularly scheduled monitoring activities, clinical research monitors will support the dynamic reporting process through their review of source document and other data information.

The BSC Medical Safety group includes physicians with expertise in electrophysiology, interventional cardiology, and/or cardiology, and with the necessary therapeutic and subject matter expertise to evaluate and classify the events into the categories outlined above.

23.2. *Steering Committee*

An Executive Committee composed of the sponsor's Clinical Management and the study Coordinating Principal Investigator(s) may be 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 request participation of OPTION Investigators on the Committee.

23.3. *Clinical Events Committee*

A Clinical Events Committee (CEC) is an independent group of individuals with pertinent expertise that reviews and adjudicates important events for inclusion into the primary and secondary endpoints. The CEC will adjudicate events for all subjects beginning at the point of randomization. The events that the CEC will review for this study include:

- All cause stroke and TIA
- Systemic embolism
- Pericardial Effusion requiring intervention
- All cause death
- ISTH major bleeding and clinically relevant non-major bleeding
- Other events, at the discretion of Boston Scientific

The CEC will review a safety event dossier, which may include copies of subject source documents provided by study centers and confirm inclusion of the event into the primary and secondary endpoints. Committee membership may include practitioners of electrophysiology, interventional cardiology, neurology, and neuroradiology. CEC responsibilities, qualifications, membership, and committee procedures are outlined in the CEC charter.

23.4. *Data Monitoring Committee*

An independent Data Monitoring Committee (DMC) will be established for the review of data and safety parameters in the study. The DMC will develop a charter and stopping rules for the study. The members will consist of at least three physicians in specialties of electrophysiology, interventional cardiology, or neurology. At least one member of the committee will be a biostatistician.

The DMC will function in accordance with Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees. Meeting frequency will be determined by the DMC to review the clinical data and assess the impact of adverse events.

24. Suspension or Termination

22.1 Premature Termination of the Study

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

22.1.1 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/REB or regulatory authorities to suspend or terminate the clinical investigation.
- An enrollment rate far below expectation that prejudices the conclusion of the study.
- A decision on the part of Boston Scientific to suspend or discontinue development of the device.

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

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

22.3. 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/REB and regulatory authorities, as applicable, will be notified. Detailed information on how enrolled subjects will be managed thereafter will be provided.

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

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

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

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

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

25. Study Registration and Results

25.1. *Study Registration*

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

25.2. *Clinical Investigation Report*

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

26. Publication Policy

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

- All authorship and contributorship requirements as described above must be followed.

- BSC involvement in the publication preparation and the BSC Publication Policy should be discussed with the Coordinating Principal Investigator(s) and/or Executive/Steering Committee at the onset of the project.
- The First and Senior authors are the primary drivers of decisions regarding publication content, review, approval, and submission.

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

27. Reimbursement and Compensation for Subjects

27.1. *Subject Reimbursement*

Travel and other expenses incurred by subjects as a result of participation in the study may be reimbursed by BSC, subject to inclusion in the study site's approved budget, approval by the study site's IRB/EC and in accordance with pertinent country laws and regulations and per the study site's regulations.

27.2. *Compensation for Subject's Health Injury*

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

28. Bibliography

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29. Abbreviations and Definitions

29.1. *Abbreviations*

Abbreviations are shown in **Table 29.1-1**.

Table 29.1-1: Abbreviations

Abbreviation	Term
ADE	Adverse Device Effect
AE	Adverse Event
AF	Atrial Fibrillation
BSC	Boston Scientific Corporation
CFAE (ablation)	Complex Fractionated Atrial Electrograms
CIP	Clinical Investigation Plan
CHF	Congestive Heart Failure
CNS	Central Nervous System
CRF	Case Report Form
CRO	Contract Research Organization
CT	Computerized Tomography
CTI (ablation)	Cavo-Tricuspid Isthmus
DAPT	Dual Antiplatelet Therapy
DFU	Directions for Use
DOAC	Direct Oral Anticoagulant (see NOAC)
EC	Ethics Committee
FMEA	Failure Mode Effects
FU	Follow-up
GI	Gastrointestinal
HA	Hazard Analysis
HAT	Hypattenuated thickening
ICE	Intra-Cardiac Echo
ICF	Informed Consent Form
IFU	Instruction for Use
IRB	Institutional Review Board
LAA	Left Atrial Appendage
LVEF	Left Ventricular Ejection Fraction
MI	Myocardial Infarction
MRS	Modified Rankin Scale
NI	Non-Inferior
NIHSS	National Institutes of Health Stroke Scale
(N)OAC	(Non-VKA) Oral Anticoagulant (see DOAC)
PFO	Patent Foramen Ovale
PDL	Peri-Device Leak
QoL	Quality of Life
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SE	Systemic Embolism
TEE	Transesophageal Echo
TTE	Trans Thoracic Echo
TIA	Transient Ischemic Attack

VKA	Vitamin K Antagonist
WM	WATCHMAN

29.2. *Definitions*

29.2.1. Valvular Atrial Fibrillation

Atrial fibrillation in the setting of moderate-to-severe mitral stenosis (potentially requiring surgical intervention) or in the presence of an artificial (mechanical) heart valve.

29.2.2. Non-Valvular Atrial Fibrillation

Atrial fibrillation in the absence of moderate-to-severe mitral stenosis or a mechanical heart valve.

29.2.3. Bleeding definitions

29.2.3.1. Bleeding Academic Research Consortium (BARC)

Type 0:
No bleeding

Type 1:
Bleeding that is not actionable and does not cause the subject to seek unscheduled performance of studies, hospitalization, or treatment by a health-care professional; may include episodes leading to self-discontinuation of medical therapy by the subject without consulting a health-care professional.

Type 2:
Any overt, actionable sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria:

- requiring nonsurgical, medical intervention by a health-care professional,
- leading to hospitalization or increased level of care, or
- prompting evaluation

Type 3:

Type 3a:

- Overt bleeding plus hemoglobin drop of 3 to < 5 g/dL(provided hemoglobin drop is related to bleed)
- Any transfusion with overt bleeding

Type 3b:

- Overt bleeding plus hemoglobin drop ≥5 g/dL(provided hemoglobin drop is related to bleed),
- Cardiac tamponade,
- Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid),
- Bleeding requiring intravenous vasoactive agents

Type 3c:

- Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal),
- Subcategories confirmed by autopsy or imaging or lumbar puncture,
- Intraocular bleed compromising vision.

Type 4:

- CABG-related bleeding,
- Perioperative intracranial bleeding within 48 h,
- Reoperation after closure of sternotomy for the purpose of controlling bleeding
- Transfusion of ≥ 5 U whole blood or packed red blood cells within a 48-h period,
- Chest tube output more than or equal to 2L within a 24-h period

Type 5:

Fatal bleeding

Type 5a:

Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious

Type 5b:

Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

(from *Circulation*. 2011; **123**(23): 2736-47)

For the purposes of the OPTION trial, a BARC score of Type 3 a, b, c and 5 a and b will be considered a major bleeding event.

29.2.3.2. ISTH

International Society on Thrombosis and Haemostasis bleeding definitions.
ISTH Clinical relevant non-major bleeding is defined as any sign or symptom of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for the ISTH definition of major bleeding but does meet at least one of the following criteria[1].

- requiring medical intervention by a healthcare professional
- leading to hospitalization or increased level of care (e.g., ER visit, diagnostic procedures, medication change)
- prompting a face to face * (i.e., Not just a telephone or electronic communication) evaluation

*such as office or telehealth visit to evaluate the event

ISTH major bleeding is defined as having a symptomatic presentation and[2].

- Fatal bleeding, and/or
- Bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, or pericardial, or intramuscular with compartment syndrome, and/or
- Bleeding causing a fall in hemoglobin level of 20 g L^{-1} (1.24 mmol L^{-1}) or more or leading to transfusion of two or more units of whole blood or red cells.

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29.2.4. Cardiac Perforation

A pericardial effusion resulting in surgical intervention/repair, regardless of whether initial attempts at non-invasive or percutaneous were attempted.

29.2.5. Left Ventricular (LV) Dysfunction

As part of the evaluation of subjects CHADS-VASc score and systolic dysfunction, referencing ESC 2020 Guidelines (Table 8)[30] below is a reference to LV dysfunction thresholds

- Severe LV Dysfunction: <35%
- Moderate LV Dysfunction: 35-40%
- Mild LV Dysfunction: 41-49%
- Normal LV Dysfunction: ≥ 50%

European Journal of Heart Failure (2012) 14, 295–301 doi:10.1093/eurjhf/hfs005

29.2.6. Mortality

Cardiovascular Death

- Death due to proximate cardiac cause, e.g., myocardial infarction, cardiac tamponade, worsening heart failure, endocarditis;
- Death caused by non-coronary, non-CNS vascular conditions such as pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular disease;
- Death from vascular CNS causes
    - From haemorrhagic stroke
    - From ischaemic stroke
- All-cause mortality during the index procedure, any procedure-related death within 30 days after the index procedure or during postoperative hospitalization for the index procedure (if >30 days). These including those related to a complication of the procedure or treatment for a complication of the procedure.

Unexplained Death

- Sudden or unwitnessed death defined as non-traumatic, unexpected fatal event occurring within one hour of the onset of symptoms in an apparently healthy subject. If death is not witnessed, the definition applies when the victim was in good health 24 hours before the event.
- Death of unknown cause.

Non-Cardiovascular Death

Any death in which the primary cause of death is clearly related to another condition (e.g., trauma, cancer, suicide).

Pericardial Effusion

Severity of pericardial effusion, with or without cardiac tamponade, is defined by the clinical therapy associated with the effusion[1]:

Clinically non-relevant

- Requiring no intervention
- Treated pharmacologically

Clinically relevant

- Treated with therapeutic pericardiocentesis
- Treated with surgical intervention
- Requiring blood transfusion
- Resulting in shock and/or death

[1] Tzikas et al. Percutaneous left atrial appendage occlusion: the Munich consensus document on definitions, endpoints, and data collection requirements for clinical studies. Europace. 2017 Jan;19(1):4-15.

29.2.7. Stroke/TIA definitions

Broad definitions:

Neurological deficit: An acute episode of a focal or global neurological deficit with at least one of the following:

- Change in the level of consciousness
- Hemiplegia
- Hemiparesis
- One-sided numbness or sensory loss
- Dysphasia or aphasia
- Hemianopia
- Amaurosis fugax
- Any other neurological signs or symptoms consistent with stroke

In addition, there are no other readily identifiable non-stroke cause for the clinical presentation (e.g., brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacologic influences), to be determined by or in conjunction with the designated neurologist.

Stroke: Stroke is defined by either one of the following:

- Duration of focal or global neurological deficit >24 h.
- Duration of focal or global neurological deficit <24 h in case of imaging-documented new hemorrhage or infarct.
- A neurological deficit resulting in death.

Transient ischemic attack: A TIA is defined by any neurological deficit not satisfying the above criteria for stroke, specifically a deficit lasting <24 h without imaging-documented new hemorrhage or infarct.

Stroke diagnostic criteria:

- Rapid onset of a focal or global neurological deficit with at least one of the following: change in level of consciousness, hemiplegia, hemiparesis, numbness or sensory loss affecting one side of the body, dysphasia or aphasia, haemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke;
- Duration of a focal or global neurological deficit ≥24 h; OR, 24 h, 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 (MR or CT scan or cerebral angiography)
    - Lumbar puncture (i.e. spinal fluid analysis diagnostic of intracranial hemorrhage)

Stroke Types:

Ischemic: An episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction

Hemorrhagic:

- intracerebral: rapidly developing clinical signs of neurological dysfunction attributable to a focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma.
- Subarachnoid: rapidly developing signs of neurological dysfunction and/or headache because of bleeding into the subarachnoid space (the space between the arachnoid membrane and the pia mater of the brain or spinal cord), which is not caused by trauma.
- NOTE: hemorrhagic transformation of a known ischemic stroke will be considered an ischemic stroke.

Silent infarction: Imaging or neuropathological evidence of CNS infarction, without a history of acute neurological dysfunction attributable to the lesion.

Stroke caused by cerebral venous thrombosis: Infarction or hemorrhage in the brain, spinal cord, or retina because of thrombosis of a cerebral venous structure. Symptoms or signs caused by reversible edema without infarction or hemorrhage do not qualify as stroke.

Not otherwise specified: an episode of acute neurological dysfunction presumed to be caused by ischemia or hemorrhage, persisting ≥ 24 hours or until death, but without sufficient evidence to be classified as one of the above
(from Kappetein, A.P., et al., J Am Coll Cardiol, 2012. **60**(15): p. 1438-54)

Disabling stroke:
an mRS score of 2 or more at 90 days and an increase in at least one mRS category from an individual's pre-stroke baseline

Non-disabling stroke:
a stroke that results (at 90 days after stroke onset) in an mRS score of > 2, or that does not result in an increase in ≥1 mRS category from an individual's pre-stroke baseline

29.2.8. Systemic Embolism

Acute vascular insufficiency or occlusion of the extremities or any non-CNS organ associated with clinical, imaging, surgical/autopsy evidence of arterial occlusion in the absence of other likely mechanism (e.g., trauma, atherosclerosis, or instrumentation). When there is presence of prior peripheral artery disease, angiographic or surgical or autopsy evidence is required to show abrupt arterial occlusion.

29.2.9. Procedure related Complications

The occurrence of one of the following events between the time of implant and within 7 days following the procedure or by hospital discharge, whichever is later:

- All-cause death
- Ischemic stroke
- Systemic embolism, or
- Device- or procedure-related events requiring open cardiac surgery or major endovascular intervention such as pseudoaneurysm repair, AV fistula repair, or other major endovascular repair.

Note: Percutaneous catheter drainage of pericardial effusions, snaring of an embolized device, thrombin injection to treat femoral pseudoaneurysm and nonsurgical treatments of access site complications are excluded from this definition

29.2.10. Oral Anticoagulant Compliance

Patients who are on NOAC ≥80% of the time will be considered as being compliant to OAC therapy.