Protection against Embolism for non-valvular AF Patients: Investigational Device Evaluation of the WATCHMAN FLX™ LAA Closure Technology

PINNACLE FLX
CLINICAL TRIAL

CLINICAL INVESTIGATION PLAN

G150200

Sponsored By

Boston Scientific Corporation

300 Boston Scientific Way

Marlborough, MA 01752

This protocol contains confidential information for use by the Investigators and their designated representatives participating in this clinical investigation. The protocol should be held confidential and maintained in a secure location.

Do not copy or distribute without written permission from Boston Scientific Corporation.

Contact Information

Role	Contact
Clinical Contact	Robert Shipley, Ph.D. Fellow, Clinical Science Boston Scientific WATCHMAN 300 Boston Scientific Way Marlborough, MA 01752 (508) 683-4000
Coordinating Principal Investigators	Dr. Saibal Kar Cedars Sinai Medical Center (310) 423-3977 8631 West Third Street Room 415E Los Angeles, CA 90048 karsk@cshs.org Dr. Shephal Doshi Pacific Heart (310) 829-7678 2001 Santa Monica Blvd Suite 280 West Santa Monica, CA 90404 skdoshi@pacificheart.com
Vendors/Labs	A list of vendors/laboratories involved in the trial is maintained by the sponsor. A complete listing of applicable vendors will be provided to investigational sites.

Original Release: August 17, 2015

Current Version: April 12, 2018

Revision History

Revision Number	Release Date	Section	Change	Reason for Change
AA	14-Dec-2015	All	Revised the document to alpha	IDE approval
AB	18-Dec, 2015	12	Change method of calculation for the rate of the Primary Effectiveness Endpoint to exclude implant failures from rate denominator.	FDA input.
		9	Changed the echo exclusion criteria of pericardial effusion > 2mm to > 5mm (and/or other criteria listed in 9.4)	National PI feedback based on experience in previous WATCHMAN trials. The change will avoid unnecessarily excluding subjects in the trial
		20	Clarifications	Editorial
		25	Added a section for CMS	Required for IDE coverage
		8	Decreased sites participating from up to 40 to up to 35	Site selection complete
AC	12-Jan-2016	8	Increased the number of sites from up to 35 to up to 40	Align with IDE approval
	13-Jan-2016	12	Corrected secondary endpoint hypothesis	Typo
AD	27-Jan-2016	9	Added exclusion for pregnant subjects	Clarification
AE	7-MAR-2016	9	Added $CHADS_2$ score and Increased CHA_2DS_2-VASc score to 3	Based on the national coverage decision (NCD)
		2	Added Access system as test device for Japan only	Clarification
		11	Updated medication regimen section	Clarification

Revision History

Revision Number	Release Date	Section	Change	Reason for Change
AF	12-APR-2018	11	Added DOAC as the post implant drug regimen	Study WM with most widely used anticoagulants
		All	Removed Japan and made minor clarifications throughout	US only trial
		8	Increased number of sites to 45 and roll-ins to 90	Requirement of 2 roll-ins per site
		9	Inclusion criteria changed from CHA_2DS_2-VASc 3 or greater to CHA_2DS_2-VASc 2 or greater for males or CHA_2DS_2-VASc 3 or greater for female	Align with IDE approval Study Design Consideration

2. Protocol Synopsis

PINNACLE FLX: Protection against Embolism for non-valvular AF Subjects: Investigational Device Evaluation of the WATCHMAN FLX™ LAA Closure Technology	
Objective(s)	The primary objective of this study is to establish the safety and effectiveness of the WATCHMAN FLX™ Left Atrial Appendage Closure (LAAC) Device for subjects with non-valvular atrial fibrillation who are eligible for anticoagulation therapy to reduce the risk of stroke.
Planned Indication(s) for Use	The WATCHMAN FLX Device is 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 $CHADS_2$ or CHA_2DS_2-VASc scores and are recommended for anticoagulation therapy; • Are deemed by their physicians to be suitable for anticoagulation therapy; and • Have an appropriate rationale to seek a non-pharmacologic alternative to anticoagulation therapy, taking into account the safety and effectiveness of the device compared to anticoagulation therapy.
Test Device	The WATCHMAN FLX Left Atrial Appendage Closure Device with Delivery System (consisting of the Delivery Catheter with a pre-loaded Closure Device)
Device Sizes	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.
Study Design	This study is a prospective, non-randomized, multi-center investigation to establish the safety and effectiveness of the WATCHMAN FLX LAAC Device for subjects with non-valvular atrial fibrillation who are eligible for long-term anticoagulation therapy to reduce the risk of stroke but who have a rationale to seek a non-pharmacologic alternative.
Planned Number of Subjects	A maximum of 490 subjects will be enrolled in the study.
Planned Number of	Up to 45 investigational centers in the United States.

PINNACLE FLX: Protection against Embolism for non-valvular AF Subjects: Investigational Device Evaluation of the WATCHMAN FLX™ LAA Closure Technology	
Centers / Countries	
Primary Effectiveness Endpoint	The rate of effective LAA closure defined as any peri-device flow ≤ 5mm demonstrated by TEE at 12 months.
Primary Safety Endpoint	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. 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 endpoint.
Secondary Effectiveness Endpoint	The occurrence of ischemic stroke or systemic embolism at 24 months from the time of implant
Additional Analysis	The occurrence of stroke (including ischemic and/or hemorrhagic), cardiovascular death (cardiovascular and/or unexplained cause) and systemic embolism.
Method of Assigning Subjects to Treatment	A subject who signs informed consent is considered enrolled in the study.
Follow-up Schedule	Study procedures and follow-up visits will occur as follows: • Enrollment Visit • WATCHMAN FLX™ Implant (within 3 calendar days of Enrollment TEE) • 45-day Follow-up (45 ± 15 days) • 6-Month Follow-up (180 ± 30 days) • 12-Month Follow-up (365 ± 30 days)

PINNACLE FLX: Protection against Embolism for non-valvular AF Subjects: Investigational Device Evaluation of the WATCHMAN FLX™ LAA Closure Technology	
	• 18-Month Follow-up (540 ± 30 days) • 24-Month Follow-up (730 ± 60 days) The study will be considered complete with regards to the primary efficacy endpoint after at least 50% of enrolled subjects complete the 18 month visit.
Study Duration	The duration of the study is expected to last approximately 38 months. The duration of individual subject participation is expected to last approximately 24 months but may vary per subject (withdrawal, death, etc.).
Required Medication Therapy	Direct oral anticoagulant (DOAC), aspirin, clopidogrel , heparin, and antibiotics, as applicable and outlined within the Directions for Use (DFU), this protocol, and institutional procedure.
Key Inclusion Criteria	1. The subject is 18 years of age or older. 2. The subject has documented paroxysmal, persistent, permanent or long-term/longstanding persistent non-valvular atrial fibrillation (i.e., the subject has not been diagnosed with rheumatic mitral valvular heart disease). 3. The subject is eligible for the defined protocol pharmacologic regimen of anticoagulation and antiplatelet therapy following WATCHMAN FLX Device implant. 4. The subject is eligible to come off of anticoagulation therapy if the LAA is sealed (i.e. the subject has no other conditions that would require long-term anticoagulation therapy suggested by current standard medical practice). 5. The subject has a calculated CHA_2DS_2-VASc score of 2 or greater for males or 3 or greater for females. 6. The subject is able to understand and 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.
Key Exclusion Criteria	1. Subjects who are currently enrolled in another investigational study or registry that would directly interfere with the current study, except when the subject is participating in a mandatory governmental registry, or a purely observational registry with no associated treatments. Each instance must be brought to the attention of the

PINNACLE FLX: Protection against Embolism for non-valvular AF Subjects: Investigational Device Evaluation of the WATCHMAN FLX™ LAA Closure Technology	
	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 anticoagulation due to other medical conditions requiring chronic anticoagulation therapy). 3. The subject is contraindicated for short-term anticoagulant therapy with DOAC post-implant. 4. The subject is contraindicated to aspirin and/or clopidogrel. 5. The subject is indicated for long-term clopidogrel therapy or has taken clopidogrel within 7 days prior to the WATCHMAN FLX™ Device implant. 6. The subject had or is planning to have any cardiac or non-cardiac invasive or surgical procedure within 30 days prior to or 60 days after the WATCHMAN FLX Device implant (including, but not limited to: cardioversion, coronary angiogram with or without percutaneous coronary intervention (PCI), cardiac ablation, cataract surgery, endoscopy, etc.). 7. The subject had a prior stroke (of any cause, whether ischemic or hemorrhagic) or transient ischemic attack (TIA) within the 90 days prior to enrollment. 8. 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 enrollment. 9. The subject has a history of atrial septal repair or has an ASD/PFO device. 10. The subject has implanted mechanical valve prosthesis in any position. 11. The subject has New York Heart Association Class IV Congestive Heart Failure at the time of enrollment. 12. 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). 13. The subject has a documented life expectancy of less than two years.
ECHO Exclusion Criteria	1. The subject has LVEF < 30%. 2. The subject has intracardiac thrombus, LAA sludge (gelatinous, non-adherent, intracavitary echo-density more layered than dense

PINNACLE FLX: Protection against Embolism for non-valvular AF Subjects: Investigational Device Evaluation of the WATCHMAN FLX™ LAA Closure Technology	
	spontaneous echo contrast (SEC) seen continuously throughout cardiac cycle) or dense SEC visualized by TEE within 3 calendar days prior to implant. 3. The subject has an existing pericardial effusion with a circumferential echo-free space > 5mm, and/or the subject has signs/symptoms of acute or chronic pericarditis, and/or there is evidence (clinically or echocardiographically) of tamponade physiology. 4. The subject has a high- risk patent foramen ovale (PFO) with an atrial septal aneurysm excursion > 15mm or length $\geq$ 15mm. 5. The subject has a high-risk PFO with a large shunt defined as early, within 3 beats and/or substantial passage of bubbles. 6. The subject has significant mitral valve stenosis (i.e., MV <1.5 cm^2). 7. The subject has complex atheroma with mobile plaque of the descending aorta and/or aortic arch. 8. The subject has a cardiac tumor.
Multiple Interventions During Index Procedure	No concomitant procedures are to be performed at the time of the WATCHMAN FLX™ implant procedure. This includes, but is not limited to, cardiac ablation procedures, transcutaneous valve procedures, cardioversions, pacemaker or ICD generator change, etc.

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 two primary endpoints must be met. The details of each endpoint analysis are listed in the table below.

Endpoint	Assessment period	Expected Rate	Delta	Performance Goal	Min/Max Observable rate	Test (α=5%)	Expected
Primary Effectiveness	12-month follow-up visit	99.3%	2.3%	97.0%	98.8%	One-sided exact test	20%
Primary Safety	7 days or hospital discharge, whichever is later	1.68%	2.53%	4.21%	2.5%	One-sided exact test	0%
Secondary Effectiveness	0 to 2 yrs.	4.7%	4.0%	8.7%	6.2%	Pointwise log-log upper confidence limit of Kaplan-Meier rate	20%

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. 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].

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.

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 [6-9]. 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 [10]. 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 [11]. 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 [12]. While DOACs eliminate 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.

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™ 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 compile

real-world clinical outcomes data for the next-generation WATCHMAN™ device, WATCHMAN FLX™ LAA Closure Device, in subjects with non-valvular AF.

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™ 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.

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.

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. All devices tested in these trials utilized the WATCHMAN (Gen 2.5) Closure Device except for EVOLVE. The EVOLVE study tested safety and efficacy in what was at the time the next-generation WATCHMAN (Gen 4) device.

Table 4.2: Clinical Studies of the WATCHMAN™ Device

Study	Dates of Enrollment	Enrolled	Sites	Follow-Up

		Subjects		
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 (feasibility study)	Jan 2009 – Nov 2011	150	4	Complete
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	Ongoing through 5 years
EWOLUTION (EU registry)	Oct 2013 – May 2015	1025	47	Ongoing through 2 years
WASP (Asia Pacific Registry)	Jan 2014 – Oct 2015	201	9	Ongoing through 2 years
WATCHMAN NESTed (US PAS)	Dec 2016-present	2000	All commercial sites	Ongoing through 5-years
SALUTE (Japan study)	Feb 2017-July 2017	71	10	Ongoing through 2 years
ASAP-TOO (OAC contraindicated population)	Feb 2017-present	888	Up to 100	Ongoing through 5-years

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[13] (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 most recent, published analysis of the PROTECT AF[14] 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[15] _ENREF_8 (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 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. [16] 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 (2.3 vs. 0.3 per 100 pt-years) favored to the Control group, while the hemorrhagic stroke rate (0.4 vs. 0.7 per 100 pt-years) and death (cardiovascular or unexplained) rate (1.4 vs. 2.3 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.

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 was enrolled on 25-Sep-2012. The final subjects were

enrolled on 21-Mar-2014, and are currently in long-term follow-up out to 5 years. 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 2.3%, which is in line with the other WATCHMAN trials.

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 is an observational, prospective, single-arm, multicenter clinical study (Europe, Middle East, Russia) that compiles real-world clinical outcome data for WATCHMAN LAA Closure Device in a commercial setting and collects 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 1025 patients scheduled for a WATCHMAN implant at 47 centers in 13 countries were enrolled, and subjects are being followed for two years after WATCHMAN implantation according to standard medical practice. Analyses include procedural and long-term data, including stroke/embolism, bleeding, and death.

Preliminary baseline/implant data, the results of the peri-procedural analyses, and data through the 3-month visit were presented for 1020 subjects. 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 populations 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 99.7% 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. Three patients died within 30 days of causes that 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 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.

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 study demonstrated a high procedure success with the WATCHMAN device placed in 94.0% of all procedures attempted. All cause death was the most prevalent adverse event, occurring in fourteen (14) subjects. The next most frequent event was device thrombus (8). Of the cases of device thrombus one (1) was associated with an ischemic stroke event. The remaining seven (7) events of device thrombus were treated with low molecular weight heparin until resolution. Ischemic stroke was reported in four (4) subjects for a rate of 1.5 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

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 in Japanese medical environment. Enrollment is complete and the trial is in long-term follow-up.

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. This trial began enrollment in February of 2017 and will randomize 888 subjects at up to 100 worldwide centers.

4.2.1. Initial WATCHMAN FLX EU LMR Experience

The first iteration of the WATCHMAN FLX Device began a limited market release (LMR) in Europe on November 11, 2015. This LMR continued until March 29, 2016. During this period, WATCHMAN FLX was implanted in 213 patients at 23 European centers. The LMR was not a clinical trial so clinical results were generated by survey and case review. The WATCHMAN FLX implant success rate was 94.0% (213/227) during the LMR and the adverse event rate was relatively low at 5.8% when accounting for all potential adverse events and the learning curve associated with a new device. Of interest was the overall device embolization rate of 3.8% (8/210). All embolized devices were retrieved percutaneously. The rate of embolization (3.8%) for this initial FLX iteration was greater than anticipated based on prospective risk assessment, as well as the historical rate experienced with the WATCHMAN (Gen 2.5) Device. The rate of device embolizations in the PREVAIL randomized clinical study was <0.7%.

Based on the European LMR experience with the earlier iteration of WATCHMAN FLX, Boston Scientific elected to make design enhancements to the device. These design enhancements were incorporated into the current WATCHMAN FLX Device (i.e., the device included the PINNACLE FLX trial).

5. Device Description

5.1.*Product 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.

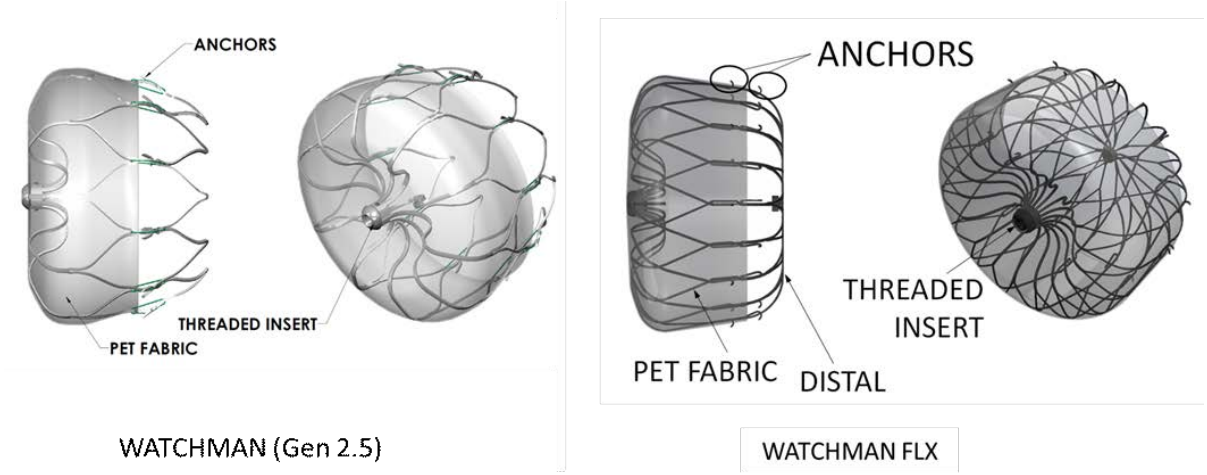
5.1.1. WATCHMAN FLX Delivery System and with Pre-loaded LAAC Device

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, similar to the currently available WATCHMAN (Gen 2.5) Device, but covers a slightly larger range from 14 to 31.5 mm. Closure Device selection is determined by LAA measurements using fluoroscopy (fluoro) and echocardiographic guidance.

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



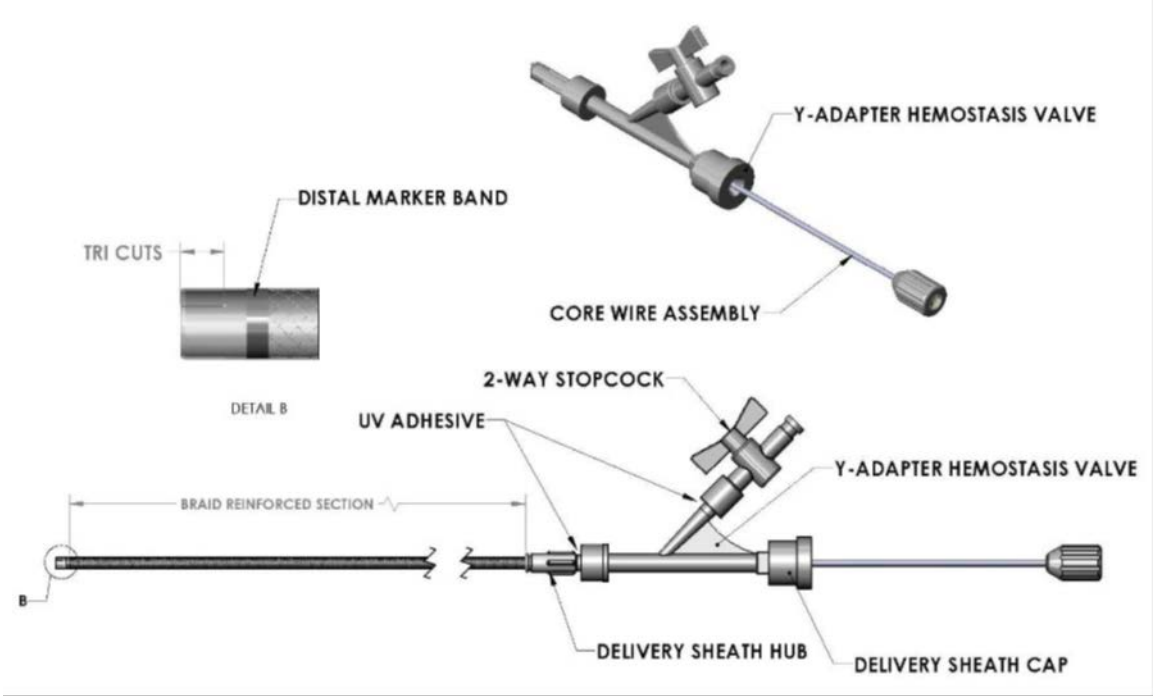
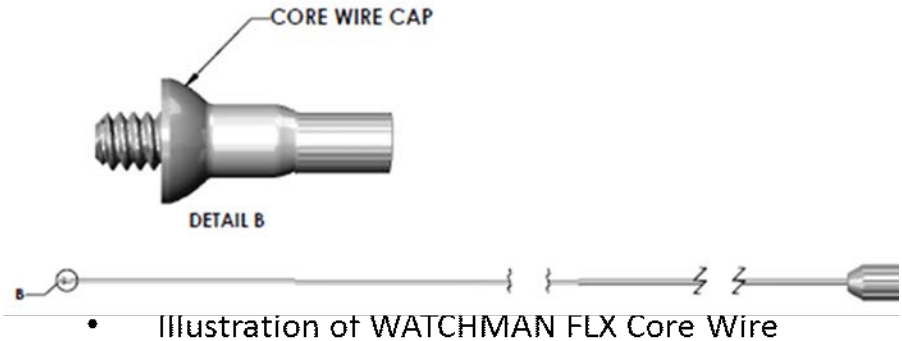


Illustration of WATCHMAN FLX Delivery Sheath Assembly



• 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 – Decreases the number of devices used and sheath exchanges per case, which may reduce procedure time and complications associated with sheath exchange.
- Decreased Recapture Force – Improves user experience.
- Increased Conformability – Creates 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 – Improves visibility under fluoroscopy.
- Shorter Device Length – Allows for treatment of shorter appendages.
- Greater Device Use Range – Provides for treatment of a wider range of appendage sizes.

5.2.*Indications for Use*

The WATCHMAN FLX Device is indicated to reduce the risk of thromboembolism from the left atrial appendage (LAA) in patients with non-valvular atrial fibrillation who:

- Are at increased risk for stroke and systemic embolism based on $CHADS_2$ or CHA_2DS_2-VASc scores and are recommended for anticoagulation therapy;
- Are deemed by their physicians to be suitable for anticoagulation therapy; and
- Have an appropriate rationale to seek a non-pharmacologic alternative to anticoagulation therapy, taking into account the safety and effectiveness of the device compared to anticoagulation therapy.

Contraindications

Do not use the WATCHMAN FLX Device if:

1. Intracardiac thrombus is visualized by TEE echocardiographic imaging.
2. An atrial septal defect repair or closure device or a patent foramen ovale repair or closure device is present.
3. The LAA anatomy will not accommodate a Closure Device (refer to the WATCHMAN FLX Device Selection guide in the WATCHMAN FLX DFU).
4. The patient has a known hypersensitivity to any portion of the device material or the individual components (see Device Description in the WATCHMAN FLX DFU) such that use of the WATCHMAN FLX Device is contraindicated.
5. Any of the customary contraindications for other percutaneous catheterization procedure (e.g. patient size too small for TEE probe or required catheters) or conditions (e.g., active infection, bleeding disorder) is present.

6. There are contraindications to the use of anticoagulation, aspirin, or clopidogrel .

6. Study Objectives

The primary objective of this study is to establish the safety and effectiveness of the WATCHMAN FLX™ Left Atrial Appendage Closure Device for patients with non-valvular atrial fibrillation who require treatment for potential thrombus formation. The WATCHMAN FLX™ Device is intended 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 who are eligible for anticoagulation therapy.

7. Study Endpoints

7.1. *Primary Effectiveness Endpoint*

The rate of effective closure defined as any peri-device flow ≤ 5mm demonstrated by TEE at 12 months.

7.2. *Primary Safety Endpoint*

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 will be captured as adverse events (AEs), and are excluded from this endpoint.

7.3. *Secondary Effectiveness Endpoint*

The occurrence of ischemic stroke or systemic embolism at 24 months from the time of implant.

7.4. *Additional analysis*

The occurrence of stroke (including ischemic and/or hemorrhagic), cardiovascular death (cardiovascular and/or unexplained cause) and systemic embolism.

8. Study Design

This study is a prospective, non-randomized, multi-center investigation to establish the safety and effectiveness of the WATCHMAN FLX™ LAA Closure Device for subjects with non-valvular atrial fibrillation who require treatment for potential thrombus formation.

This study will be conducted at up to 45 centers in the United States. Of the potential 490 subjects, 400 will be enrolled in the main cohort. The remaining 90 subjects will be Roll-in subjects.

Investigators will include physicians with WATCHMAN (Gen 2.5) implant experience. Sites will be limited to two implanting investigators per institution. All sites are required to enroll two Roll-in subjects prior to enrollment in the main cohort of subjects. The use of Roll-in subjects will allow physicians to gain experience with the WATCHMAN FLX implant procedure prior to beginning enrollment in the main study cohort.

8.1. *Scale and Duration*

Subjects will be followed through the enrollment period, at device implant, then at intervals of 45 days, 6 months, 12 months, 18 months and 24 months,

It is anticipated that enrollment will be conducted over a period of 12 months.

8.2. *Treatment Assignment*

The study is designed to enroll subjects that meet all inclusion and no exclusion criteria.

8.3. *Justification for the Study Design*

The WATCHMAN LAA Closure Device with Delivery System and WATCHMAN Access System received FDA approval on March 13, 2015 and received CE mark on October 5, 2005. WATCHMAN FLX was chartered to enhance the user experience and acute safety profile for the WATCHMAN LAA Closure Technology compared to the current WATCHMAN LAAC Device (also called WATCHMAN Gen 2.5). The PINNACLE FLX investigational device exemption (IDE) study is designed to collect safety and effectiveness data on the next-generation WATCHMAN Device (called WATCHMAN FLX). The implant of the Closure Device will be done according to the current indications and under direction of the WATCHMAN FLX DFU. Acute procedure-related information will be collected to assess safety; long-term follow-up visits at 12, 18, and 24 months will be used to assess long-term safety and effectiveness.

9. Subject Selection

9.1. *Study Population and Eligibility*

Any subject who provides written informed consent is enrolled in the study. The subjects selected for participation will be from the investigators' general subject population. The investigator has the responsibility for screening all potential subjects and selecting those who meet study inclusion criteria and do not meet any of the exclusion criteria as described in sections 9.2 and 9.3. There are additional Echo exclusion criteria (section 9.4) that must be met. All subjects will have their screening criteria assessed such that the baseline TEE is the final determination of eligibility.

9.2. *Inclusion Criteria*

Subjects who meet all of the following criteria (Table 9-1) will be given consideration for inclusion in this clinical investigation, provided no exclusion criterion (see Section 9.3) is met.

Table 9-1: Inclusion Criteria

Clinical Inclusion Criteria	1. The subject is 18 years of age or older. 2. The subject has documented paroxysmal, persistent, permanent or long-term/longstanding persistent non-valvular atrial fibrillation (i.e., the subject has not been diagnosed with rheumatic mitral valvular heart disease). 3. The subject is eligible for the defined protocol pharmacologic regimen of anticoagulation and antiplatelet therapy following WATCHMAN FLX Device implant. 4. The subject is eligible to come off of anticoagulation therapy if the LAA is sealed (i.e. the subject has no other conditions that would require long-term anticoagulation therapy suggested by current standard medical practice). 5. The subject has a calculated CHA_2DS_2-VASc score of 2 or greater for males or 3 or greater for females. 6. The subject is able to understand and 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 criteria (Table 9-2) will be excluded from this clinical study.

Table 9-2: Exclusion Criteria

Clinical Exclusion Criteria	1. Subjects who are currently enrolled in another investigational study or registry that would directly interfere with the current study, except when the subject is participating in a mandatory governmental registry, or a purely observational registry with no associated treatments. Each instance must be brought to the attention of the sponsor to determine eligibility, 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 anticoagulation due to other medical conditions requiring chronic anticoagulation therapy). 3. The subject is contraindicated for short-term anticoagulant therapy with DOAC post-implant. 4. The subject is contraindicated to aspirin and/or clopidogrel. 5. The subject is indicated for long-term clopidogrel therapy or has taken clopidogrel within 7 days prior to the WATCHMAN FLX Device implant. 6. The subject had or is planning to have any cardiac or non-cardiac invasive or surgical procedure within 30 days prior to or 60 days after the WATCHMAN FLX Device implant (including, but not limited to: cardioversion, coronary angiogram with or without percutaneous coronary intervention (PCI), cardiac ablation, cataract surgery, endoscopy, etc.). 7. The subject had a prior stroke (of any cause, whether ischemic or hemorrhagic) or transient ischemic attack (TIA) within the 90 days prior to enrollment. 8. 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 enrollment. 9. The subject has a history of atrial septal repair or has an ASD/PFO device. 10. The subject has implanted mechanical valve prosthesis in any position. 11. The subject has New York Heart Association Class IV Congestive Heart Failure at the time of enrollment. 12. 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). 13. The subject has a documented life expectancy of less than two years.

9.4. *Echo Exclusion Criteria*

After informed consent and prior to or at the onset of procedure a TTE/TEE is performed. These additional exclusion criteria must be evaluated for each subject. If any of the Echo exclusion criteria are met, then the subject will be withdrawn from the study and will be classified as "INTENT" subject.

Table 9-3: Echo Exclusion Criteria

Echo Exclusion Criteria	1. The subject has LVEF < 30%. 2. The subject has intracardiac thrombus, LAA sludge (gelatinous, non-adherent, intracavitary echo-density more layered than dense spontaneous echo contrast (SEC) seen continuously throughout cardiac cycle) or dense SEC visualized by TEE within 3 calendar days prior to implant. 3. The subject has an existing pericardial effusion with a circumferential echo-free space > 5mm, and/or the subject has signs/symptoms of acute or chronic pericarditis, and/or there is evidence (clinically or echocardiographically) of tamponade physiology. 4. The subject has a high- risk patent foramen ovale (PFO) with an atrial septal aneurysm excursion > 15mm or length $\geq$ 15mm. 5. The subject has a high-risk PFO with a large shunt defined as early, within 3 beats and/or substantial passage of bubbles. 6. The subject has significant mitral valve stenosis (i.e., MV <1.5 cm^2). 7. The subject has complex atheroma with mobile plaque of the descending aorta and/or aortic arch. 8. The subject has a cardiac tumor

10. Subject Accountability

10.1. *Point of Enrollment*

Subjects who have signed and dated the Informed Consent Form are considered enrolled in the study. The implant visit must occur within 30 days of informed consent and within 3 days of LAA imaging.

10.2. *Withdrawal (point of study exit)*

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.

If a subject withdraws from the clinical investigation, the reason(s) must be reported. If such withdrawal is due to problems related to the WATCHMAN FLX 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.

Reasons for study exit include, but are not limited to, 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 reason, and without prejudice to further treatment.

The sponsor may ask that withdrawn subjects be followed for information related to the safety of the WATCHMAN FLX™ device if available. If such withdrawal is due to problems related to investigational device safety or performance, the investigator shall ask for the subject's permission to follow his/her status/condition outside of the clinical study.

Study subjects may also complete the study per protocol requirements. When that has occurred, their participation in the study is considered as complete, and they will have exited the study.

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 three documented attempts to contact them prior to completion of the "End of Study" form. 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 open 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 investigational device, these should be followed through resolution.

10.3. *Subject Status and Classification*

10.3.1. Screen Failure

A subject who signs informed consent, but does not meet clinical eligibility criteria is considered a screen failure. ***These subjects do not count towards the enrollment ceiling and will not be used for the primary analysis***. Screen failure subjects should be withdrawn immediately upon determining ineligibility. The original signed Informed Consent must be maintained in the center's subject file and the following forms must be completed:

- Enrollment forms such as, but not limited to: informed consent, enrollment information and other related forms

10.3.2. Intent

A subject who signs informed consent, meets clinical eligibility criteria, but then does not undergo an implant of a WATCHMAN FLX Device will be classified as "Intent." This definition includes subjects that do not meet LAA imaging eligibility criteria for a WATCHMAN FLX Device at the implant TEE/CT evaluation (e.g. a thrombus has developed in the LAA, inappropriate LAA size). This definition also includes subjects in which anticoagulation has been changed or interrupted prior to the WATCHMAN FLX implant (prior to the WATCHMAN Access Sheath being inserted into the body for implant),

but ultimately do not undergo an implant. Intent subjects must be followed until the 45 day visit from the time of intervention. Adverse events (AE) related to the protocol required interventions (e.g. TEE and/or protocol required medication change) must be recorded on the AE form. For these subjects, the follow-up may occur via phone or in-office visit. TEE and NIHSS is not required for INTENT subjects at the 45-day follow-up.

Intent subjects do not count towards the enrollment ceiling and will not be used for the primary analysis. They will be included in a sensitivity analysis.

The original signed Informed Consent must be maintained in the center's subject file and the following forms must be completed:

- Enrollment forms such as, but not limited to: informed consent, enrollment information and other related forms
- "Adverse Event" form(s) for any reportable event, as defined in Section 20 for any adverse event that occurs after signing the Informed Consent, up to the point of subject withdrawal
- 45 Day Visit Form(s);
- An "End of Study" form must be completed following the 45 day visit

10.3.3. Attempt

A subject who signs informed consent and 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 will be followed until the 45 day visit and adverse events will be collected up to the point of subject withdrawal. This information can be collected via a phone or in-office visit. Attempt subjects count towards the enrolment ceiling and will be used for analyses of the endpoints. The original signed Informed Consent must be maintained in the center's study file and the following forms must be completed: TEE and NIHSS is not required for ATTEMPT subjects at the 45-day follow-up.

- Enrollment forms such as, but not limited to: informed consent, screening, Enrollment information and other related forms;
- Implant forms, such as, but not limited to: device information, procedure information and other related forms;
- 45 Day Visit Form(s);
- Adverse Event and/or Device Deficiency form(s) for any reportable event(s), as defined in Section 20; and
- "End of Study" form for withdrawal, when applicable.

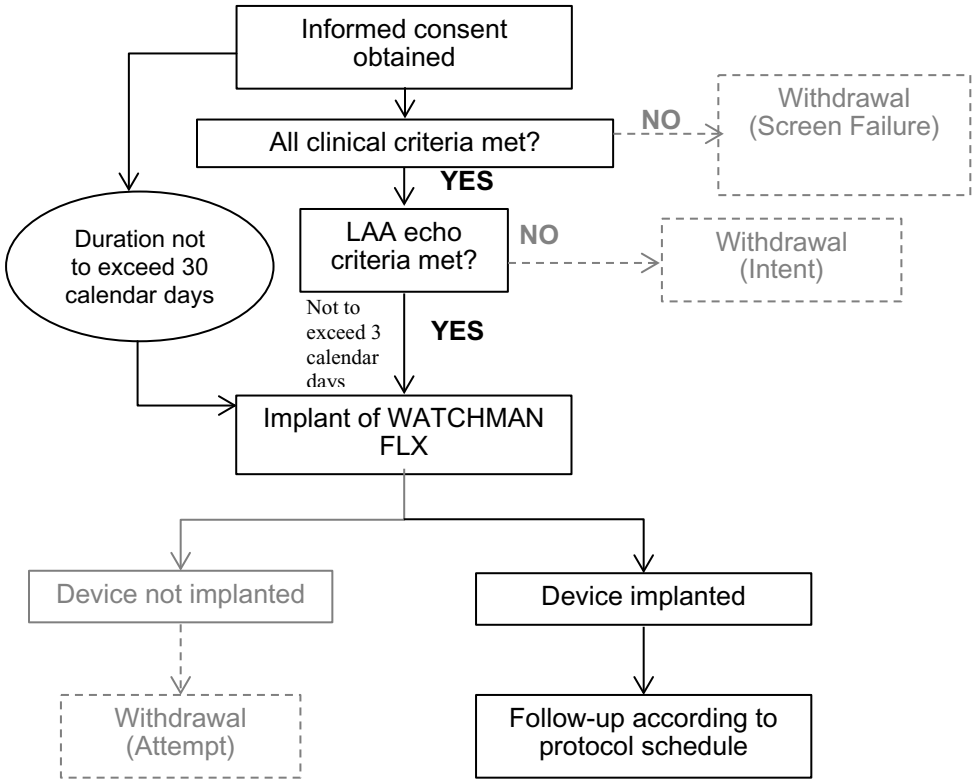
The date at which the "End of Study" form has been completed will be considered as the point of subject withdrawal.

10.3.4. 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 and included in all study analyses. 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 center's subject file.

Figure 2: Subject Status and Data Collection Flow Chart

10.4. *Enrollment Controls*



Subject enrollment into the WATCHMAN FLX Study will be discontinued upon attempting 400 non-roll-in subjects with the WATCHMAN FLX Device. Investigational sites will be notified when the enrollment goal is close to being reached and once enrollment is complete.

11. Study Methods

11.1. *Data Collection*

For subjects classified as INTENT or ATTEMPT (underwent the testing or implant procedure but DID NOT receive the WATCHMAN FLX Device), all visits up to and

including the 45 day visit are required. All AE reporting should also be completed. LAA imaging or NIHSS is not required for these subjects.

For all IMPLANT subjects (successfully received the WATCHMAN FLX Device) all visits are required, as defined in Table 11-1.

Table 11-1: Data Collection Schedule

Procedure/Assessment	Enrollment	Implant	Follow-up Visits				
			45-Day (± 15 Days) Office or Phone Visit[e]	6-Month (180 days ± 15 Days) Office Visit	12 months (365 days ± 30 Days) Office Visit	18 months (540 days ± 30 Days) Office Visit	24 Month (730 days ± 60 Days) Office Visit
Informed consent form, including informed consent signature date	X						
Demographics, including age, gender, and race and ethnicity	X						
Physical exam including vital signs	X		X[c]	X	X	X	X
Medical history	X						
Transthoracic echocardiogram (TTE)[a]	X						
Transesophageal echocardiogram (TEE)	X[b]	X	X[c]	X[g]	X		
Brain Imaging (MRI/CT)	X[d]		As required[f]	As required[f]	As required[f]	As required[f]	As required[f]
Anticoagulant and antiplatelet medications	X		X	X	X	X	X
Modified Rankin Scale	X		X[c]	X	X	X	X
NIH Stroke Scale	X		X[c]		X		X
Device and implant details		X					
Adverse event/ Device Deficiency monitoring	X	X	X	X	X	X	X
Hemoglobin, eGFR[h,] and proteinuria	X						

[a] An LVEF value obtained from a TTE performed within 90 days prior to enrollment may be used. If a significant cardiac event occurs after the TTE which causes a change in cardiac status [i.e., major Congestive Heart Failure (CHF) decompensation] the enrollment TTE must be repeated at enrollment

[b] Within 3 calendar days prior to implant

[c] For Intent and Attempt not required

[d] Obtain MRI/CT required at baseline if subject had prior stroke or TIA. A MRI or CT performed within in 90 days prior to enrollment may be used.

[e] For Intent and Attempt subjects the visit can be performed in office or via phone. For subjects classified as implant an office visit is required

[f] Brain MRI or CT required if subject suffers stroke or TIA

[g] Only required for subjects that did not have a seal at the 45-day visit

[h] eGFR obtained up to 6 months prior to enrollment may be used

12. Informed Consent

12.1. *Informed Consent*

In order to determine eligibility of a subject, the investigator needs to implement the consent process and verify and document that the subject meets the inclusion/exclusion criteria. Informed consent is required from all subjects prior to the subject's participation in the study. The subject should be given ample time to consider participation and ask questions if necessary. An IRB-approved informed consent form must be signed and personally dated by the subject or his/her legal representative. The original, signed document is to be kept with the subject's file and a copy must be provided to the subject. The informed consent process must be documented by the person obtaining consent and the documentation must be placed in the subject's file. The implant visit must occur within 30 calendar days of informed consent for study participation.

12.2. *Enrollment Visit*

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

Subjects who have signed and dated the Informed Consent Form are considered enrolled. The implant visit must occur within 30 calendar days of enrollment. Once LAA imaging eligibility is confirmed, the implant visit must occur within 3 calendar days.

The following will be assessed at the Enrollment visit and documented on the case report forms for enrolled subjects:

- Demographics and medical history
- Physical exam including vital signs
- Current medication regimen for the use of antiplatelet and anticoagulation medications
- Modified Rankin Scale (MRS) and NIH Stroke Scale (NIHSS)
- Subjects with prior history of ischemic stroke, hemorrhagic stroke or TIA are required to have a Baseline MRI or CT obtained (up to 90 days prior to consent or at the enrollment visit if no prior measurement is available)
- Transesophageal echocardiogram (TEE) within three calendar days of implant (can occur at the time of implant).
- Transthoracic Echocardiogram (TTE) (up to 90 days prior to consent or at enrollment if no prior measurement is available)

- Hemoglobin
- eGFR (serum creatinine up to 6 months before enrollment or at enrollment if no prior measurement is available)
- Proteinuria (dichotomized as protein none/trace vs. 1+ or higher)

12.3. *Stroke Assessments*

The Modified Rankin Scale (MRS) score will be routinely collected at Enrollment and office follow-up visits for all subjects and should be collected at 90 (+/- 10) days following a stroke or TIA event. This scale assesses the severity of stroke disability and functional dependence of subjects. This test will be collected at baseline and all office follow-up visits. The assessment must be performed by either a neurologist or personnel who have completed a certification for the MRS.

The NIH Stroke Scale (NIHSS) is an assessment tool which quantifies stroke related neurological deficit. This assessment must be conducted in person to provide valuable information on stroke severity. This test will be performed at baseline, at 45 days, 12 months, 24 months and if possible, following stroke. It must be conducted by a neurologist or personnel who have a current certification to conduct the NIHSS.

12.4. *LAA Imaging (e.g. Fluoro/TEE/TTE)*

TEE imaging and fluoroscopy are required during the WATCHMAN implant procedure to assist the investigator to appropriately guide the WATCHMAN System Access Sheath into the LAA, obtain proper measurements of the LAA to correctly size the device, and to ensure appropriate device position. CT imaging of the LA is occasionally performed for pre-planning of LAAC with WATCHMAN. This is not required for this study and does not replace the need for the enrollment/implant TEE. However, if CT is performed, sites must note this on the data collection form and the image should be saved to disk and available to the sponsor upon request.

After informed consent, all subjects will undergo an enrollment TEE and TTE. For subjects successfully implanted with the WATCHMAN FLX Device, follow-up TEE's at the 45-day visit, 6-month visit (if applicable), and 12 month visit are also required. All study required TEEs will be performed by protocol trained individuals and in accordance with the Imaging Manual. Copies of the TEE's will be sent to the Echo Core Lab per the Imaging Manual. Fluoroscopy recordings and images may be recorded and made available to the sponsor upon request.

Copies of all protocol required TEE imaging will be saved to disk and available to the sponsor upon request. Certain information from TEEs conducted during the course of the study, including any non-protocol required TEEs, will be captured on the study case report forms. The site and subject identification number should be clearly identified on the disks.

Copies of the Enrollment TTE imaging will be saved to disk and available to the sponsor upon request. Certain information from TTEs conducted during the course of the study will

be captured on the study case report forms. The site and subject identification number should be clearly identified on the disks.

i) Transthoracic Echocardiogram (TTE)

All TTEs will be conducted according to the Imaging Manual if required. The Enrollment TTE will be done to evaluate LVEF to confirm subject eligibility. An LVEF value obtained from a TTE performed within 90 days prior to enrollment may be used. If a significant cardiac event occurs after the TTE which causes a change in cardiac status [i.e., major Congestive Heart Failure (CHF) decompensation] the enrollment TTE must be repeated after informed consent and prior to implant.

ii) Transesophageal Echocardiogram (TEE)

All protocol required TEEs will be performed by protocol trained individuals and in accordance with the Imaging Manual. The Enrollment TEE will determine that all inclusion and exclusion criteria are met. The implant must occur within three calendar days of the enrollment TEE. The enrollment TEE may occur on the same day as implant. The implant TEE 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, and confirm adverse events have not occurred during the implant procedure (i.e., pericardial effusion).

The 45-day, 6-month (if applicable) and 12-month TEEs are conducted to assess flow through and around the WATCHMAN FLX Device and to verify there is no thrombus on the surface of the device. Adequate LAA seal is defined as little or no visible residual blood flow around the margins of the WATCHMAN FLX Device in either a retrograde or antegrade fashion, with jet size ≤ 5mm.

As required by protocol, some subjects may also have a 6-month TEE if the 45-day TEE demonstrates inadequate seal around the device or device thrombus.

a. Stroke or Systemic Embolism TEE

In the event that a subject experiences a stroke or systemic embolism (SE) during the course of the study (see section **20.8**), supporting TEE documentation will be requested by the sponsor in an attempt to search for causes of stroke or embolic event. If a stroke or SE occurs, a TEE is strongly encouraged to help better ascertain the mechanism of the stroke or SE. An optimal TEE evaluation includes, where feasible based on subject status and technical considerations, evaluation of:

i. LA thrombus – size, location, mobility, etc.

ii. WATCHMAN FLX Device seal or presence (and measurement) of peri-device flow

iii. WATCHMAN FLX Device thrombus or pannus – size, location, mobility, etc.

iv. 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)

v. Presence, location and grade of ascending and arch aortic atheroma

vi. Presence of worsening left ventricular dysfunction, "new" regional wall motion abnormality or presence of LV thrombus (LVEF data may be supplemented/substituted by TTE where appropriate, in addition to TEE parameters above)

b. Device Thrombus TEE

The most accurate determination of whether thrombus has formed on the surface of the WATCHMAN FLX™ Device is through TEE evaluation. In the case of thrombus on the atrial facing side of the device, anticoagulation therapy should be initiated for approximately 12 weeks, or a longer period of time per hospital standard of care, for treatment of thrombus. After the course of anticoagulation therapy, a repeat TEE evaluation should be performed to confirm the thrombus has resolved. Cessation of anticoagulation after this timepoint is at the discretion of the investigator.

12.5. *Implant Procedure*

The implant visit must occur within 30 calendar days of consent and within 3 calendar days of enrollment/implant LAA imaging. The implant procedure should be performed using standard of care methods established by the investigational center (e.g. sterile technique, personnel requirements, etc.). Implantation of the WATCHMAN FLX Device should only be performed by physicians trained in percutaneous and transseptal procedures who have completed the WATCHMAN physician training program and WATCHMAN FLX implant training. Refer to the WATCHMAN FLX Directions for Use (DFU) for detailed instructions regarding the implantation and use of the WATCHMAN FLX Device.

Information collected during the implant procedure includes the following:

- WATCHMAN FLX Device usage information
- Access System(s) usage information
- Device Release Criteria
- Device Deficiencies
- Device-, procedure- and/or study-related adverse events experienced since previous visit

12.6. *Study Medication Regimen (for subjects classified as Implant)*

Protocol-required concomitant medications must be reported in the eCRF from the time of the enrollment visit through the 2 year follow-up. Information pertaining to the use of oral anticoagulants, clopidogrel, and aspirin, including dose changes, medication interruptions, and medication cessation, must be documented.

- **Implant through 45-Day TEE**

Following device placement, anticoagulation with a direct oral anticoagulant (DOAC) must be started and should be administered in accordance with the Directions for Use per the specific DOAC prescribed.. Implanted subjects should be on DOAC therapy through at least the 45-day follow-up. Use of apixaban or rivaroxaban is strongly recommended though other FDA approved DOACs can be used if necessary. While on DOAC therapy, subjects should also be prescribed aspirin (81-100mg). Aspirin is necessary post device placement to mitigate platelet aggregation. Subjects should remain on DOAC and aspirin until the 45-day TEE evaluation has shown adequate seal of the LAA.

- **45-Day Visit**

A TEE will be conducted at the 45-day visit to assess position and the seal around the perimeter of the WATCHMAN FLX Device within the LAA ostium. Adequate LAA seal is defined as little or no visible residual blood flow around the margins of the WATCHMAN FLX Device in either a retrograde or antegrade fashion, with jet size $\leq$ 5mm.

If the 45-day TEE shows adequate seal of the LAA with a jet around the device $\leq$ 5mm:

- DOAC therapy should be discontinued,
- Aspirin (81-100 mg) should be continued indefinitely, and
- Clopidogrel (75mg) should be initiated, taken for 6-months post-implant, and then discontinued.

If the 45-day TEE shows inadequate seal of residual LAA blood flow with a jet size > 5mm around the margins of device, the subject should remain on anticoagulation therapy and aspirin and a future TEE (i.e. 6 months post-implant) should be conducted to assess LAA seal as determined by the investigator.

Cessation of OAC therapy is at physician discretion provided that any peri-device flow demonstrated by TEE is $\leq$ 5 mm. If adequate seal is not demonstrated, subsequent OAC therapy cessation decisions are contingent on demonstrating flow $\leq$ 5 mm. At the time the patient ceases OAC therapy, the patient should continue aspirin and begin clopidogrel daily. This regimen should continue until 6 months have elapsed after implantation. Patients should then remain on aspirin indefinitely. If a patient remains on OAC therapy and aspirin (81 mg-

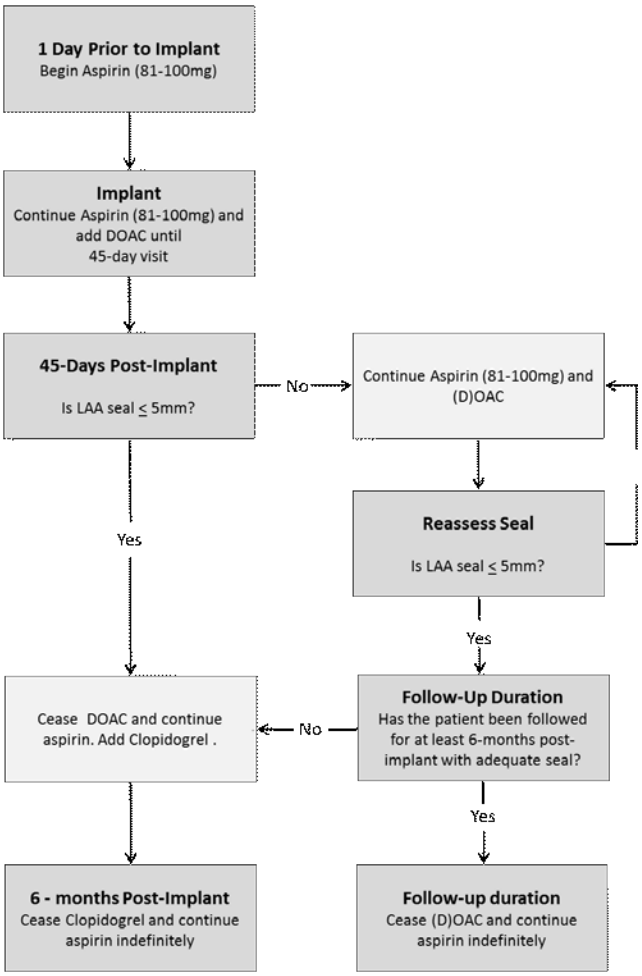
100 mg) for at least 6 months after implantation, and then ceases OAC therapy, the patient should not require clopidogrel, but should continue aspirin daily.

Clopidogrel may be substituted with ticagrelor or prasugrel if the subject requires the medication for other indications (e.g. acute coronary syndromes treated with drug eluting stents) or if the subject cannot take clopidogrel. Prasugrel should only be used if neither clopidogrel nor ticagrelor can be used due to potential for increased bleeding risk.

Notes:

- Do not use prasugrel in patients with active pathological bleeding or a history of transient ischemic attack or stroke.
- In patients ≥75 years of age, prasugrel is generally not recommended, except in high-risk patients (diabetes or prior MI), where its use may be considered.
- Additional risk factors for bleeding with prasugrel include: body weight <60 kg; propensity to bleed; concomitant use of medications that increase the risk of bleeding.
- Do not use ticagrelor in patients with a history of intracranial bleeding

Figure 3: WATCHMAN FLX Device Implant Pharmacologic Regimen



12.7. *Follow-up Procedures*

12.7.1. Follow-Up (45-Days)

12.7.1.1. For Subjects classified as Intent or Attempts

Subjects who were NOT successfully implanted with the WATCHMAN FLX Device will complete an office or phone visit 45-days post procedure/intervention (i.e. TEE and/or NIHSS for Intent or Attempt not required). Information collected during the 45-day visit for "INTENT" or "ATTEMPT" subjects includes the following:

Device, procedure and/or study related adverse events experienced since previous visit
TEE, MRS, physical exam, vital signs, or NIHSS is not required for these subjects

12.7.1.2. For Subjects classified as Implants

Subjects successfully implanted with the WATCHMAN FLX Device will complete an office visit 45-days post-implant with a TEE evaluation. Information collected during the 45-day visit includes the following:

TEE (as described in Section 11.5)
Modified Rankin Score and NIH Stroke Scale (NIHSS)
Current medication regimen for the use of antiplatelet and anticoagulation medications (as described in Section 11.7)
Physical exam including vital signs
Device-, procedure- and/or study-related serious adverse events, including device deficiencies experienced since previous visit
Stroke, SE and/or Thrombus TEE, if needed and not available from time of last event
Brain MRI or CT follow-up if needed and not available from time of last event

A TEE will be conducted at the 45-day visit to assess position and the seal around the perimeter of the WATCHMAN FLX Device within the LAA ostium. Adequate LAA seal is defined as little or no visible residual blood flow around the margins of the WATCHMAN FLX Device in either a retrograde or antegrade fashion, with jet size $\leq$ 5mm.

12.7.2. Office Visit Follow-up (6-month+/- 15 days)

All subjects classified as Implant should complete the 6 month visit. Subjects whose 45-day TEE demonstrates inadequate seal around the device or device thrombus should have an additional TEE at 6-months to assess position and the seal around the perimeter of the WATCHMAN FLX Device within the LAA ostium. Adequate LAA seal is defined as little or no visible residual blood flow around the margins of the WATCHMAN FLX Device in either a retrograde or antegrade fashion, with jet size $\leq$ 5mm

Information collected during the 6-month visit includes the following:

TEE (as described in Section 11.5) for subjects who do not have a device seal at 45 days. Subjects who had a device seal at 45 days do not require at TEE at 6 months.
Modified Rankin Score
Current medication regimen for the use of antiplatelet and anticoagulation medications (as described in Section 11.7)
Physical exam including vital signs
Device-, procedure- and/or study-related adverse events, including device deficiencies experienced since previous visit

Stroke, SE and/or Thrombus TEE, if needed and not available from time of last event
Brain MRI or CT follow-up if needed and not available from time of last event

12.7.3. Office Visit Follow-up (12-month+/- 30 days)

Subjects will complete an office visit 12-months post-implant. Information collected during this visit includes the following:

TEE (as described in Section 11.5)
Modified Rankin Score and NIH Stroke Scale (NIHSS)
Current medication regimen for the use of antiplatelet and anticoagulation medications (as described in Section 11.7)
Physical exam including vital signs
Device-,, procedure- and/or study-related adverse events, including device deficiencies experienced since previous visit
Stroke, SE and/or Thrombus TEE, if needed and not available from time of last event
Brain MRI or CT follow-up if needed and not available from time of last event

12.7.4. Office Visit Follow-Up (18-months+/- 30 days)

Subjects will complete an office visit 18-months post-implant. Information collected during this visit includes:

Modified Rankin Scale
Current medication regimen for the use of antiplatelet and anticoagulation medications
Physical exam including vital signs
Device, procedure and/or study related adverse events, including device deficiencies experienced since previous visit
Stroke, SE and/or Thrombus TEE, if needed and not available from time of last event
Brain MRI or CT follow-up if needed and not available from time of last event

12.7.5. Office visit Follow-Up (24-months)

Subjects will complete an office visit 24 months post implant. Information collected during this visit includes:

Modified Rankin Score and NIH Stroke Scale (NIHSS)
Current medication regimen for the use of antiplatelet and anticoagulation medications
Physical assessment including vital signs
Device-, procedure- and/or study-related serious adverse events, including device deficiencies experienced since previous visit
Stroke, SE and/or Thrombus TEE, if needed and not available from time of last event
Brain MRI or CT follow-up if needed and not available from time of last event

12.8. *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 eCRF's to complete.

Type of Study Exit	**Date to Use**	**Form(s) to complete**
Subject withdrawal	Date of subject withdrawal	End of Study form Adverse Event (resolve/close any AE's)
Subject Lost to Follow-up	The date of last attempt to contact the subject	End of study form Adverse Event (resolve/close any AE's)
Subject Death	Date of Death	End of Study Form Adverse Event with fatal outcome, resolve/close other AE's (only one event to be recorded with outcome of fatal)
Complete all protocol visits	Date of last study visit	End of Study Form Adverse Event (resolve/close any AE's)

13. Statistical Considerations

13.1. *Endpoints*

13.1.1. Primary Effectiveness Endpoint

The rate of effective closure defined as any peri-device flow ≤ 5mm demonstrated by TEE at the 12 months visit.

13.1.1.1. Hypotheses

H_0: $P_{e1} \leq 97.0\%$
H_1: $P_{e1} > 97.0\%$
where P_{e1} is the Primary Effectiveness Endpoint rate.

13.1.1.2. Sample Size

A sample size of 400 enrolled subjects is required to evaluate the 1st Primary Effectiveness Endpoint, accounting for 20% attrition. This sample size was calculated employing exact binomial methodology using SAS version 9.4 with the following assumptions:

Expected rate of effective LAA closure = 99.3%
Delta = 2.3%
Performance goal = 97.0%
1-sided alpha = 5%
Power = 92%
Expected attrition rate = 20%

Required sample size = 400 subjects

The expected rates of effective LAA closure and attrition are based off the rates observed in the combined PREVAIL and CAP2 WATCHMAN subjects with a $CHADS_2$ score ≥ 2 or a CHA_2DS_2-VASc score ≥ 3 (July 9, 2015 update), which were 99.3% and 20%, respectively. The attrition estimate includes all patients who do not have a 12-month TEE performed. A delta of 2.3% was then subtracted from the expected rate of effective LAA closure to establish the performance goal of 97.0%. This represents a minimum observable rate of 98.8%, which is similar to the rate observed in previous WATCHMAN studies.

13.1.1.3. Statistical Methods

All implanted subjects with a completed 12-month TEE, and who have not had any LAA closure procedures other than the initial FLX implant attempt, will be considered for the endpoint analysis. All subjects who complete their 12-month TEE will be included in the denominator for the Primary Effectiveness event rate. All subjects who complete the 12-month TEE and demonstrate a peri-device flow of ≤ 5mm will be included in the numerator. A one-sided exact binomial test will be used to test the assumption that the rate of effective LAA closure at 12 months is > 97.0%. The null hypothesis will be rejected if the resulting p-value is less than 0.05.

13.1.2. Primary Safety Endpoint

The Primary Safety Endpoint is 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. Events included into this endpoint will be confirmed by CEC adjudication. Percutaneous catheter drainage of pericardial effusions, snaring of an embolized device, thrombin injection to treat femoral pseudoaneurysm and minor nonsurgical treatments of access site complications are excluded from this endpoint. .

Hypotheses

H_0: $P_s \geq 4.21\%$
H_a: $P_s < 4.21\%$
where P_s is the rate of subjects experiencing a safety endpoint event within 7 days or hospital discharge, whichever is later

13.1.2.1. Sample Size

A sample size of 400 subjects is required to evaluate the Primary Safety Endpoint. This sample size was calculated employing exact binomial methodology using SAS version 9.4 with the following assumptions:

Expected event rate = 1.68%
Delta = 2.53%
Performance goal = 4.21%
1-sided alpha = 5%
Power = 92%
Expected attrition rate = 0%
Required sample size = 400 subjects

The expected rate of the Primary Safety Endpoint is based off the rate observed in the combined PREVAIL and CAP2 WATCHMAN subjects with a $CHADS_2$ score ≥ 2 or a CHA_2DS_2-VASc score ≥ 3 (July 9, 2015 update), which was 1.68%.. A delta of 2.53% was then added to this expected rate to establish the performance goal of 4.21%. This performance goal corresponds to a maximum observable rate of 2.5%, and is deemed to be clinically acceptable based on observed rates of procedural complications in comparable procedures.

13.1.2.2. Statistical Methods

The Primary Safety event rate will be calculated as the percent of all implanted or attempted subjects who experience a Primary Safety event. A one-sided exact binomial test will be used to test the null hypothesis that the rate of subjects experiencing a Primary Safety event

is ≥ to 4.21% vs the 1-sided alternative hypothesis that the rate is <4.21%. The null hypothesis will be rejected if the resulting p-value is less than 0.05.

13.1.3. Secondary Effectiveness Endpoint

The Secondary Effectiveness End point is the occurrence of ischemic stroke or systemic embolism at 24 months from the time of implant. Events included into this endpoint will be confirmed by CEC adjudication.

13.1.3.1. Hypotheses

H_0: $P_{e2} \geq 8.7\%$
H_1: $P_{e2} < 8.7\%$
where P_{e2} is the 2-year Kaplan-Meier rate of the Secondary Effectiveness Endpoint.

13.1.3.2. Sample Size

A sample size of 400 enrolled subjects is required to evaluate the Secondary Primary Effectiveness Endpoint, accounting for 20% attrition. This sample size was calculated employing exact binomial methodology and confirmed via Monte Carlo simulations employing Kaplan-Meier methodology, using SAS version 9.4 with the following assumptions:

Expected event rate = 4.7%
Delta = 4.0%
Performance goal = 8.7%
1-sided alpha = 5%
Power = 90%
Expected attrition rate = 20%

Required sample size = 400 subjects

The expected rate of the Secondary Effectiveness Endpoint is based off the rate observed in PREVAIL-eligible subjects with a $CHADS_2$ score ≥ 2 or a CHA_2DS_2-VASc score ≥ 3 from the combined PROTECT AF, CAP, PREVAIL and CAP2 WATCHMAN arms (July 9, 2015 update), which was 4.7%.The 20% expected rate of attrition accounts for all subjects who exit the study for any reason, including death, prior to 2 years. A delta of 4.0% was added to the expected event rate to establish the performance goal of 8.7%. This corresponds to a maximum observable rate of 6.2%.

The performance goal of 8.7% is considered clinically meaningful in the context of the expected ischemic stroke rate for a population eligible for this study but treated only with aspirin (ASA). This expected rate was determined from the Swedish Atrial Fibrillation Cohort study of approximately 182,000 subjects [17]. The risk of ischemic stroke for a given subject out of a population of 1000 subjects followed for one year are tabulated below based on the subject's CHA_2DS_2-VASc Score. It is assumed that the annual rate would be linear out to two years. Thus, the annual stroke risk per 1000 subject-years was doubled and then divided by 10 to convert the 2-year stroke rate.

CHA_2DS_2-VASc Score	**Annual Stroke Risk/1000 Subject-years**	**2-Year Stroke Rate**
1	0.6	1.2%
2	25	5.0%
3	37	7.4%
4	55	11.0%
5	84	16.8%

A linear regression was calculated for the two year stroke rate as a function of CHA_2DS_2-VASc score to yield the following equation:

$$\text{2-year stroke rate} = CHA_2DS_2\text{-VASc score} * 3.72 - 2.88;\ r^2 = 0.977$$

The mean CHA_2DS_2-VASc score observed in PREVAIL-eligible subjects from the combined PROTECT AF, CAP, PREVAIL, and CAP2 studies was 4.3. Substituting a CHA_2DS_2-VASc score of 4.3 into the equation yields an expected 2-year ischemic stroke rate of 13.1% for subjects treated with ASA only. Therefore the performance goal of 8.7% represents an improvement over ASA only for the Secondary Primary Effectiveness Endpoint, which includes systemic embolism events in addition to ischemic stroke.

13.1.3.3. Statistical Methods

Data from all implanted or attempted subjects at the time of endpoint analysis will be eligible for inclusion in this endpoint analysis. The Secondary Effectiveness event rate from date of implant (or date of attempt, for devices attempted but not implanted) through 2 years post-implant will be calculated using Kaplan-Meier methodology. Event-free subjects who exit the study will be censored at the time of their last follow-up. The 95% one-sided upper pointwise confidence limit of the event rate will be calculated via log-log methodology for all eligible subjects contributing to the analyses and compared to the performance goal of 8.7%. If the upper confidence limit is less than 8.7%, the null hypothesis will be rejected.

13.2. *General Statistical Methods*

13.2.1. Analysis Sets

The analysis set for the Primary Effectiveness analysis includes implanted subjects with a completed 12-month TEE, and who have not had any LAA closure procedures other than the initial FLX implant attempt. The analysis set for the Primary Safety and Secondary Effectiveness analyses will be the "intent-to-treat" analysis set, including all implanted or attempted subjects. Roll-in subjects are excluded from all Primary and Secondary endpoint 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 important endpoints and relevant adverse events.

A tipping-point analysis may be conducted for the Primary Effectiveness Endpoint to assess the impact of different assumptions about the missing data on interpretation of the results. Specifically, for subjects who do not have evaluable 12-month TEE results, the proportion of those subjects assumed to have effective LAA closure will be varied until the point that significance compared to the performance goal no longer holds in order to assess the robustness of the conclusion of the Primary Effectiveness Endpoint analysis.

13.2.3. Control of Type-I Error

Due to the requirement that each applicable endpoint must be passed, each applicable endpoint can be tested at the significance level of 5% while still maintaining the overall type-I error level at no greater than 5%. This follows the methodology of the Intersection-Union Test (IUT). All study endpoints will be analyzed using one-sided significance levels of 5%.

13.2.4. Number of Subjects per Investigative Site

To avoid any center effect and bias, one center will not be authorized to implant or attempt more than 20% of the 400 subjects (n = 80) per this protocol without prior approval from Boston Scientific.

13.3. *Additional Data Analyses*

The following sections describe additional data analyses planned for PINNACLE FLX.

13.3.1. Justification of Pooling

Poolability across investigational center will be assessed for all Primary and Secondary Endpoints. Poolability of the Primary Effectiveness and Safety Endpoints across investigations center will be assessed by adding center into a logistic regression model as a

random effect. Centers will be deemed to be heterogeneous if the variance of the random center effect is found to be significantly different from zero using a significance level of 0.15. Poolability of the Secondary Effectiveness Endpoint across investigations center will be assessed by adding center to a shared frailty model as a random effect. 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. Regardless of the results of the poolability analyses, results by investigational center will be provided for each Primary and Secondary Endpoint.

Poolability of the Secondary Effectiveness Endpoint will be assessed across subjects who did vs did not switch from Warfarin to a DOAC upon enrollment in the study. A Cox regression model of time to ischemic stroke or SE will be fit on OAC history (switched from Warfarin to DOAC vs not) as well as CHA_2DS_2-VASc score. Results will be considered poolable if the resulting p-value for the coefficient for OAC history is ≥0.15.

13.3.2. Subgroup Analyses

Descriptive statistics will be presented for primary, secondary, and additional endpoints for the subgroups listed below:

- Sex (Female vs. Male)
- Age at time of consent (< 75 years vs. ≥ 75 years)
- Full recaptures (0 vs. ≥ 1)
- Partial recaptures (0 vs. ≥ 1)
- Risk (CHA_2DS_2-VASc Score)
- Post-implant drug regimen
- OAC history (i.e. did subject switch from Warfarin to DOAC or not upon enrollment in the study)

13.3.3. Multivariable Analyses

Univariate and multivariate modeling analyses will be performed to assess the effect of baseline covariates on the Primary Effectiveness, Secondary Effectiveness, and Primary Safety Endpoints. Logistic regression will be used to assess the effects of possible predictors on the Primary Effectiveness and Safety Endpoints, and Cox proportional hazards regression will be used to assess the effects of possible predictors on the Secondary Effectiveness Endpoint in a time-to-event manner. The covariates to be included in this analysis will include, but are not limited to, the following:

- Gender
- Ethnicity
- Age
- LAA dimension
- LAA shape
- LVEF%

- Prior stroke
- $CHADS_2$ score
- CHA_2DS_2-VASc score
- HAS-BLED score
- Medication history
- Years on anticoagulation therapy
- Cardiovascular Disease History (CAD, diabetes, hypertension)
- Cardiac Surgery History
- Significant Non-Cardiovascular Disease History
- Atrial Fibrillation History
- Full device recapture rate (0 vs. ≥ 1)
- OAC history (i.e. did subject switch from Warfarin to DOAC or not upon enrollment in the study)

13.3.4. Other Analyses

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

Administrative analyses of safety data may be performed for regulatory agency review.

Descriptive statistics of subject demographic and baseline characteristics will be presented for the overall study population.

13.3.5. Changes to Planned Analyses

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

14. Data Management

14.1. *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 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 EDC system and will be issued to the site for appropriate response. Site staff will be responsible for resolving all queries in the database.

14.2. *Data Retention*

The Investigator or Investigational Site will maintain, securely store, in original format all essential study documents and source documentation that support the data collected on the study subjects in compliance with ICH/GCP guidelines. Documents must be retained for at least 2 years after the last approval of a marketing application or until at least 2 years have elapsed since the formal discontinuation of the clinical investigation of the product. These documents will be retained for a longer period of time by agreement with BSC or in compliance with other local regulations. It is BSC's responsibility to inform the Investigator when these documents no longer need to be maintained. The Investigator will take measures to ensure that these essential documents are not accidentally damaged or destroyed. If for any reason the Investigator 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.

14.3. *Core Laboratories*

An independent core laboratory will be utilized to review TEE imaging collected at protocol required time points during the study. All interpretations of TEE 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.

Imaging will be collected by each study site according to the Imaging Protocol and submitted to the Core Lab for review. The Core Lab will provide Boston Scientific with summary of results for reporting purposes and associated study endpoint analyses.

15. Amendments

If a protocol revision is necessary which affects the rights, safety or welfare of the subject or scientific integrity of the data, an amendment is required. Appropriate approvals (e.g., IRB /FDA) of the revised protocol must be obtained prior to implementation.

16. Deviations

An Investigator must not make any changes to or deviate from this protocol, except in order to protect the life and physical well-being of a subject in an emergency. An investigator shall notify the sponsor and the reviewing IRB/EC of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency and those deviations which affect the scientific integrity of the clinical 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 the appropriate eCRF. Sites may also be required to report deviations to the IRB/EC, per local guidelines and government regulations.

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

17. Device/Equipment Accountability

The investigational devices 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 from shipment of investigational devices to the investigation sites until return or disposal.

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

The principal investigator or an authorized designee shall 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 to sponsor of unused, expired, or malfunctioning investigational devices, if applicable.

Please note: Written procedures may be required by local, state, and/or federal regulations.

Current sponsor processes will be used to track subjects and investigational device during the study. Upon completion of enrollment into the study, or as directed by the sponsor, all unused investigational devices must be returned to the sponsor.

18. Compliance

18.1. *Statement of Compliance*

This study will be conducted in accordance with 21 CFR 814.20 part 56, part 50 and part 812 or 813, ISO 14155: Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice, the relevant parts of the ICH Guidelines for Good Clinical Practice, ethical principles that have their origins in the Declaration of Helsinki, and pertinent individual country laws and regulations. The study shall not begin until the required approval/favorable opinion from the IRB/EC and/or regulatory authority has been obtained, if appropriate. Any additional requirements imposed by the IRB/EC or regulatory authority shall be followed, if appropriate.

18.2. *Investigator Responsibilities*

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

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

- Prior to beginning the study, sign the Clinical Study Agreement and 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 center 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 on the eCRFs and in all required reports.
- Record, report, and assess (seriousness and relationship to the device/procedure) reportable adverse events and observed device deficiencies.
- Report to BSC, events per the protocol requirements, and all SAEs and device deficiencies that could have led to a SADE.
- Report to the IRB/EC and regulatory authorities any SAEs and device deficiencies that could have led to a SADE, if required by the national regulations or this protocol or by the IRB/EC, and supply BSC with any additional requested information related to the safety reporting of a particular event.
- 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 monitor and respond to questions during monitoring visits.
- Allow and support regulatory authorities and the IRB/EC when performing auditing activities.
- Ensure that informed consent is obtained in accordance with applicable laws, this protocol and local IRB/EC requirements.
- Provide adequate medical care to a subject during and after a subject's participation in a clinical study in the case of adverse events, as described in the Informed Consent Form (ICF).
- Inform the subject of the nature and possible cause of any adverse events experienced.
- Inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required.
- Provide the subject with well-defined procedures for possible emergency situations related to the clinical study, and make the necessary arrangements for emergency treatment, 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.
- Ensure that maintenance and calibration of the equipment relevant for the assessment of the clinical investigation is appropriately performed and documented, where applicable.

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 and adequate supervision of those to whom tasks are delegated. 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*

Prior to gaining Approval-to-Enroll status, the investigational site will provide to the sponsor documentation verifying that their IRB/EC is registered or that registration has been submitted to the appropriate agency, as applicable according to national/regulatory requirements.

A copy of the written IRB/EC and/or competent authority approval of the protocol (or permission to conduct the study) and Informed Consent Form, must be received by the sponsor before recruitment of subjects into the study 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.

Annual IRB/EC approval and renewals will be obtained throughout the duration of the study as required by local/country or IRB/EC requirements. Copies of the Investigator's reports and the IRB/EC 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. Only authorized BSC personnel or a BSC representative including, but not limited to Contract Research Organization (CRO) will have access to these confidential records. 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. All data used in the analysis and reporting of this study will be without identifiable reference to specific subject name.

Boston Scientific will keep subjects' identifiable personal health information (PHI) confidential in accordance with all applicable laws and regulations. Boston Scientific may use subjects' personal health information to conduct this research, as well as for additional purposes, such as overseeing and improving the performance of its device, new medical research and proposals for developing new medical products or procedures, and other business purposes. 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.

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

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

Boston Scientific personnel will not do the following:

- Practice medicine.
- Provide medical diagnosis or treatment to subjects.
- Discuss a subject's condition or treatment with a subject without the approval and presence of the HCP.
- 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

A combination of on-site, remote and central monitoring will be utilized by the sponsor through the duration of the study to assess participating sites' continued compliance with the protocol and applicable local and federal regulations, The sponsor will assess and verify that study records are adequately maintained, that study 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 Investigator/institution guarantees access to original source documents by BSC personnel, their designees, and appropriate regulatory authorities.

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

20. Potential Risks and Benefits

20.1. *Anticipated Adverse Events*

Potential procedural risks associated with the WATCHMAN FLX implant procedure are similar to those encountered peri- and post-operatively for WATCHMAN (Gen 2.5) and many routine catheterization procedures. These are included in Table 19.1,

- **Table 20-1: Anticipated Adverse Events**

• Air embolism • Airway trauma • Allergic reaction to contrast media/medications or device materials • Altered mental status • Anemia requiring transfusion • Anesthesia risks • Angina • Anoxic encephalopathy • Arrhythmias • Atrial septal defect • AV fistula • Bruising, hematoma or seroma • Cardiac perforation • Chest pain/discomfort • Confusion post procedure • Congestive heart failure • Contrast related nephropathy • Cranial bleed • Death	• 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

• Decreased hemoglobin • Deep vein thrombosis • Device embolism/migration • Device fracture • Device thrombosis • Edema • Excessive bleeding • Fever • Groin pain • Groin puncture bleed • Hematuria • Hemoptysis	• Respiratory insufficiency / failure • Surgical removal of the device • Stroke – Ischemic • Stroke – Hemorrhagic • Systemic embolism • TEE complications (throat pain, bleeding, esophageal trauma) • Thrombocytopenia • Thrombosis • Transient ischemic attack (TIA) • Valvular 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 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
- 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. *Possible Interactions with Concomitant Medical Treatments*

Subjects who receive the WATCHMAN FLX Device may stop anticoagulation therapy as early as the 45-day follow-up visit if they meet anticoagulaiton 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.

20.4. *Risk Minimization Actions*

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

20.5. *Anticipated Benefits*

No direct subject benefit is expected from this study. Subjects enrolled in this study will receive the same clinical care as subjects who are routinely implanted with a WATCHMAN Device and not enrolled in this study. However, results from the data collected during this study may improve the management of WATCHMAN FLX subjects in the future; therefore, the subjects enrolled in this study may also benefit at a later stage.

WATCHMAN FLX was chartered to enhance the user experience and acute safety profile for the WATCHMAN LAA Closure Technology compared to the current 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 anticoagulation therapy may reduce bleeding complications, such as hemorrhagic stroke, associated with long-term anticoagulation. Economic and subject benefits related to the elimination of life-long compliance to anticoagulation therapy and the frequent blood tests and lifestyle changes associated with blood thinning medications are numerous.

20.6. *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 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*

Any reportable event(s), experienced by the study subject after enrollment, must be recorded in the electronic data capture system. It is the responsibility of the investigator to determine the clinical significance of the event and report the event per protocol requirements.

For the purpose of this study, relevant reportable events are defined as:

- WATCHMAN FLX Device procedure-related adverse events (see AE table 19.1).
- Adverse events related to protocol required testing (i.e., TTE, TEE).
- 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 thrombus, embolization, erosion, etc.).
- 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.
- Device deficiencies
- All serious adverse events, including: death of all cause (cardiovascular, non-cardiovascular, and unknown)
- Unanticipated adverse device effects/unanticipated serious adverse device effects not previously defined in the physician's manuals

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/procedure/protocol required testing, it should be submitted as an adverse event and/or device deficiency.

Death should not be recorded as an AE, but should only be reflected as an outcome of ONE (1) specific SAE.

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

21.2. *Definitions and Classification*

In order to provide clarity, the adverse event definitions are provided in Table 20.2-1. Administrative edits were made to the event definitions from ISO 14155-2011 and 21 CFR 812.

Table 21.2-1: Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in

Table 21.2-1: Definitions

Term	Definition
Ref: ISO 14155 *Ref: MEDDEV 2.7/3*	subjects, users or other persons, whether or not related to the investigational medical device. (see section 20.1) NOTE 1: This includes events related to the investigational medical device or comparator. NOTE 2: This definition includes events related to the procedures involved (any procedure in the clinical investigation plan).
Adverse Device Effect (ADE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Adverse event related to the use of an investigational medical device NOTE 1: This definition includes any adverse event resulting from insufficient or inadequate instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device. NOTE 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.
Serious Adverse Event (SAE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Adverse event that: • Led to death, o Led to serious deterioration in the health of the subject as defined by a life-threatening illness or injury, or o a permanent impairment of a body structure or a body function, or o in-patient-hospitalization or prolongation of existing hospitalization, or o medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function • Led to fetal distress, fetal death, or a congenital abnormality or birth defect. Note 1. Planned Hospitalization for pre-existing condition, or a procedure required by the clinical investigational plan, without a serious deterioration in health, is not considered a serious adverse event
Serious Adverse Device Effect (SADE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. NOTE 1: This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device. NOTE 2: This definition includes any event resulting from use error or intentional abnormal use of the investigational medical device.
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.

Table 21.2-1: Definitions

Term	Definition
Unanticipated Serious Adverse Device Effect (USADE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report. **NOTE 1**: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.
Device Deficiency *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	A device deficiency (DD) is any inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. **NOTE 1**: Device deficiencies include malfunctions, misuse or use errors, and inadequate labeling.

Term	Definition
Complication	An adverse event that resulted in: death, serious injury a, correction using invasive intervention, or permanent loss of device functions. a Per 21 CFR 803.3: Serious injury means an injury or illness that: • Is life-threatening • Results in permanent impairment of a body function or permanent damage to a body structure, or • Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure Permanent means irreversible impairment or damage to a body structure or function, excluding trivial impairment or damage b Invasive interventions are those in which treatment necessary to correct the adverse event is delivered by cutting or piercing of the skin or placing an instrument in a body cavity to provide therapy. Examples of invasive interventions (complication) include, but are not limited to: • Electrophysiology study in which an ablation is performed • Angiogram in which angioplasty or stent placement is performed • Intravenous medications • Blood transfusions • Intubation to provide respiratory support • Chemical (pharmacologic) cardioversion with IV sedation (This is a complication due to the IV antiarrhythmic medication used for the cardioversion.) Invasive procedures that are purely diagnostic in nature should not be considered as a complication. Some examples of procedures that are invasive, but not considered to be an intervention include: • Blood draw for laboratory analysis • Cardiac catheterization in which pressures are recorded, but without therapeutic intervention • Electrophysiology study to map arrhythmias, but without therapeutic intervention • Transesophageal echo (TEE) Electrical (external) cardioversion with IV sedation (the IV sedation used is for subject comfort and not part of the treatment)
Observation	An adverse event that was transient or reversible and corrected with non-invasive interventions, such as reprogramming or oral medications, or else resolved with no intervention or monitoring.

21.3. *Relationship to Study Device*

The Investigator must assess the relationship of the AE to the study device or. See criteria in Table 20.3-1:

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

Classification	Description
Not Related	Relationship to the device or procedures can be excluded when: - the event is not a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has no temporal relationship with the use of the 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	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	The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.
Probably Related	The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained.

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

Classification	Description
Causal Relationship	The serious event is associated with the investigational device or with procedures beyond reasonable doubt when: - the event is a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has a temporal relationship with investigational device use/application or procedures; - the event involves a body-site or organ that o the investigational device or procedures are applied to; o 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 20.4-1.

Table 21.4-1: Investigator Reporting Requirements

Event Classification	Communication Method	Communication Timeline pre-market studies* (MEDDEV 2.7/3: CLINICAL INVESTIGATIONS: SERIOUS ADVERSE EVENT REPORTING UNDER DIRECTIVES 90/385/EEC AND 93/42/EEC)
Unanticipated Adverse Device Effect / Unanticipated Serious Adverse Device Effect	Complete AE eCRF page with all available new and updated information.	• Within 1 business day of first becoming aware of the event. • Terminating at the end of the study
	Provide all relevant source documentation (de-identified) for reported event	• At request of the sponsor
Serious Adverse Event	Complete AE eCRF page with all available	• Within 3 calendar days of first becoming aware of the event or sooner as per local/regional regulations.

Table 21.4-1: Investigator Reporting Requirements

Event Classification	**Communication Method**	**Communication Timeline pre-market studies*** (MEDDEV 2.7/3: CLINICAL INVESTIGATIONS: SERIOUS ADVERSE EVENT REPORTING UNDER DIRECTIVES 90/385/EEC AND 93/42/EEC)
	new and updated information.	• Reporting required through the end of the study
	Provide all relevant source documentation (de-identified) for reported event upon request of the sponsor	• At request of sponsor
Serious Adverse Device Effects	Complete AE eCRF page with all available new and updated information.	• Within 3 calendar days of first becoming aware of the event or as per local/regional regulations. • Reporting required through the end of the study
	Provide all relevant source documentation (de-identified) for reported event	• When documentation is available
Device Deficiencies (including but not limited to failures, malfunctions, and product nonconformities) Note: Any Investigational Device Deficiency that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable event.	Complete DD form with all available new and updated information.	• Within 3 calendar days of first becoming aware of the event. • Reporting required through the end of the study
	Provide all relevant source documentation (de-identified) for reported event	• At request of sponsor
Adverse Event including Adverse Device Effects	Complete AE eCRF page, which contains such information as date of AE, treatment of AE resolution, assessment of seriousness and relationship to the device.	• In a timely manner (e.g. Recommend within 10 business days) after becoming aware of the information • Reporting required through end of study

Table 21.4-1: Investigator Reporting Requirements

Event Classification	Communication Method	Communication Timeline pre-market studies* (MEDDEV 2.7/3: CLINICAL INVESTIGATIONS: SERIOUS ADVERSE EVENT REPORTING UNDER DIRECTIVES 90/385/EEC AND 93/42/EEC)	
	Provide all relevant source documentation (de-identified) for reported event	• At request of sponsor	

Abbreviations: AE=adverse event; CRF=case report form; IDE=Investigational Device Exemption; UADE=unanticipated adverse device effect

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

21.5. *Boston Scientific Device Deficiencies (DDs)*

All device deficiencies (including but not limited to failures, malfunctions, use errors, product nonconformities, and labeling errors) will be documented and reported to BSC. If possible, the device(s) should be returned to BSC for analysis. Instructions for returning the investigational device(s) will be provided. I Device deficiencies should also be documented in the subject's source records.

Device deficiencies are to be reported as Device Deficiencies not as Adverse Events. However, if there is an adverse event that results from a device deficiency, that specific event would be recorded on the appropriate eCRF.

Additionally, any Investigational Device Deficiency that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable event.

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

BSC is responsible for reporting adverse event information to all participating investigators and regulatory authorities. In addition, data/interim reports will be provided to regulatory agencies during the course of the study.

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

21.7. *Clinical Event Committee Events (CEC) – Documentation*

As an Independent CEC will be adjudicating events for this study, appropriate medical records from investigative sites must be sent to Boston Scientific.

Events which require source documents include:

- Stroke (all causes) including TIA
- All deaths throughout the study
- Systemic embolism
- Major open cardiac and/or endovascular surgery through 7 days or hospital discharge (whichever is later)
- Major bleeding events (defined as BARC 3 or BARC 5 events)
- Other adverse events, at the discretion of Boston Scientific

21.7.1. Stroke Reporting Documentation Recommendations

In the event that a subject experiences a stroke or SE during the course of the study, supporting documentation will be requested by the sponsor. This information may include neurologist consultation note(s), MRI/CT imaging, radiology reports, additional NIHSS/MRS/Barthel Index evaluations, or statement from the investigator. In addition, a search for alternative causes of stroke (including hypercoagulable work-up) and TEE evaluation at the time of any stroke or embolic event is strongly encouraged to help better ascertain the mechanism of all strokes. An optimal TEE evaluation includes, where feasible based on subject status and technical considerations, evaluation of:

- LA thrombus – size, location, mobility, etc.
- WATCHMAN FLX Device Seal or presence (and measurement) of peri-device flow
- WATCHMAN FLX Device thrombus or pannus – 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 and grade of ascending and arch aortic atheroma
- Presence of worsening left ventricular dysfunction, “new” regional wall motion abnormality or presence of LV thrombus (LVEF data may be supplemented/substituted by TTE where appropriate, in addition to TEE parameters above)

21.8. *Device Related Thrombus*

During the course of follow-up, device-related thrombus (DRT) may be detected by cardiac imaging including TEE, CT scan and MRI scan. Based on clinical experience with the prior generation WATCHMAN Device the most accurate and reproducible determination of whether thrombus has formed on the surface of the WATCHMAN FLX Device is through TEE evaluation. TEE findings may be augmented by other confirmatory imaging modalities

In the case of DRT on the atrial facing side of the device, systemic anticoagulation therapy should be initiated for approximately 12 weeks, or a longer period of time per hospital standard of care, for treatment of thrombus. After the course of anticoagulation therapy, a repeat TEE evaluation should be performed to confirm the thrombus has resolved. Cessation of anticoagulation after this time point is at the discretion of the investigator.

21.9. *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 working days of center notification. The center's IRB must be notified of any deaths in accordance with that center's IRB policies and procedures.

Source documentation of death will include a detailed narrative (death letter) that provides detailed information describing the circumstances surrounding the death and is signed by the principal Investigator or authorized co-Investigator. For any information which may be unknown, the investigator must still address the relevant area in the detailed death narrative. A death narrative in the local language is acceptable. The death narrative must include all of the following, if available:

- Date and time of death
- Place death occurred
- Immediate cause of death
- Whether the death was related to the investigational device or clinical investigation, procedure, or subject condition
- Whether or not the death was witnessed
- Whether the subject had any Transient Ischemic Attack/Stroke/Bleeding prior to the death
- Any other circumstances surrounding the death
- Approximate time interval from the initiating event to death (temporal course)
- Investigator or co-Investigator signature and date

Any information listed above that is unavailable or unknown must be specified as unavailable or unknown, as applicable, in the narrative. Also submit the following documentation:

- A copy of the relevant medical records from enrollment to death, this will include H & P, consults, test results, operative reports, and/or progress notes from the hospital chart and clinic chart
- Death certificate (if available)
- Autopsy report (if applicable)

22. Informed Consent

Subject participation in this clinical study is voluntary. Informed Consent is required from each subject or his/her legally authorized representative when approved by the IRB and if allowed by local regulations. 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, any applicable national regulations, and local Ethics Committee and/or Regulatory authority body, as applicable. The ICF must be accepted by BSC or its delegate (e.g. CRO), and approved by the site's IRB/EC, or central IRB, if applicable.

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

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

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

The ICF shall always be signed and personally dated by the subject 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. 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 body 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), as appropriate.

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

23. Committees

23.1. *Safety Monitoring Process*

To promote early detection of safety issues, Boston Scientific reviews adverse events and device deficiencies per the Safety Plan. Events are reviewed with BSC Medical Safety. Success of this program requires dynamic collection of unmonitored data as soon as the event is reported. This is expedited through BSC's Safety Operations or it's delegate, which is responsible for coordinating the collection of information for the subject dossier from the centers and core laboratories as applicable. During regularly scheduled monitoring visits, clinical research monitors will support the dynamic reporting process through their review of source document information.

23.2. *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 events that the CEC will review for this study are the primary and secondary endpoint events and include: device and/or procedure-related events which resulted in open cardiac/endovascular surgery during the 7 days or hospital discharge (whichever is the later) period following the implant procedure. All strokes, TIA, all cause deaths, systemic embolisms, and major bleeding events will be adjudicated throughout the study. Any additional event which Safety feels requires the review of an independent

committee may also be sent. 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. CEC responsibilities, qualifications, membership, and committee procedures are outlined in the CEC charter.

23.3. *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

23.1 Premature Termination of the Study

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

23.1.1 Criteria for Premature Termination of the Study

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

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

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

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

23.3 Requirements for Documentation and Subject Follow-up

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

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

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

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

23.4 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 3 months after site initiation, or if the site has multiple or severe protocol violations/noncompliance without justification and/or fails to follow remedial actions.

In the event of termination of investigator 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 and regulatory authorities, as applicable, will be notified. All subjects enrolled in the study at the center will continue to be followed per the investigator's standard of care for subjects that undergo any WATCHMAN procedure. The Principal Investigator at the center must make provision for these follow-up visits unless BSC notifies the investigational center otherwise.

25. 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 Corporation 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.

26. Reimbursement and Compensation for Subjects

26.1. *Subject Reimbursement*

Travel and other expenses incurred by subjects as a result of participation in the study will be reimbursed in accordance with pertinent country laws and regulations and per the study site's regulations.

26.2. *Compensation for Subject's Health Injury*

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

27. Bibliography

1. Colilla S, Crow A, Petkun W, Singer DE, Simon T, Liu X. Estimates of current and future incidence and prevalence of atrial fibrillation in the u.S. Adult population. *The American journal of cardiology*. 2013;112:1142-1147
2. Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, et al. Acc/aha/esc 2006 guidelines for the management of patients with atrial fibrillation--executive summary: A report of the american college of cardiology/american heart association task force on practice guidelines and the european society of cardiology committee for practice guidelines (writing committee to revise the 2001 guidelines for the management of patients with atrial fibrillation). *J Am Coll Cardiol*. 2006;48:854-906
3. Connolly SJ, Pogue J, Eikelboom J, Flaker G, Commerford P, Franzosi MG, et al. Benefit of oral anticoagulant over antiplatelet therapy in atrial fibrillation depends on the quality of international normalized ratio control achieved by centers and countries as measured by time in therapeutic range. *Circulation*. 2008;118:2029-2037
4. Hart RG, Pearce LA, McBride R, Rothbart RM, Asinger RW. Factors associated with ischemic stroke during aspirin therapy in atrial fibrillation: Analysis of 2012 participants in the spaf i-iii clinical trials. The stroke prevention in atrial fibrillation (spaf) investigators. *Stroke*. 1999;30:1223-1229
5. White HD, Gruber M, Feyzi J, Kaatz S, Tse HF, Husted S, et al. Comparison of outcomes among patients randomized to warfarin therapy according to anticoagulant control: Results from sportif iii and v. *Arch Intern Med*. 2007;167:239-245
6. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *The New England journal of medicine*. 2009;361:1139-1151

7. Connolly SJ, Ezekowitz MD, Yusuf S, Reilly PA, Wallentin L. Newly identified events in the re-ly trial. *The New England journal of medicine*. 2010;363:1875-1876
8. Hart RG, Diener HC, Yang S, Connolly SJ, Wallentin L, Reilly PA, et al. Intracranial hemorrhage in atrial fibrillation patients during anticoagulation with warfarin or dabigatran: The re-ly trial. *Stroke*. 2012;43:1511-1517
9. FDA Drug Safety Communication: Update on the risk for serious bleeding events with the anticoagulant Pradaxa (dabigatran) FDSC. *http://www.fda.gov/Drugs/DrugSafety/ucm326580.htm*.
10. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *The New England journal of medicine*. 2011;365:883-891
11. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. *The New England journal of medicine*. 2011;365:981-992
12. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *The New England journal of medicine*. 2013;369:2093-2104
13. Reddy VY, Doshi SK, Sievert H, Buchbinder M, Neuzil P, Huber K, et al. Percutaneous left atrial appendage closure for stroke prophylaxis in patients with atrial fibrillation: 2.3-year follow-up of the protect af (watchman left atrial appendage system for embolic protection in patients with atrial fibrillation) trial. *Circulation*. 2013;127:720-729
14. Rhythm H. The heart rhythm society's 34th annual scientific sessions. 2013
15. Reddy VY, Holmes D, Doshi SK, Neuzil P, Kar S. Safety of percutaneous left atrial appendage closure: Results from the watchman left atrial appendage system for embolic protection in patients with af (protect af) clinical trial and the continued access registry. *Circulation*. 2011;123:417-424
16. Holmes DR, Jr., Kar S, Price MJ, Whisenant B, Sievert H, Doshi SK, et al. Prospective randomized evaluation of the watchman left atrial appendage closure device in patients with atrial fibrillation versus long-term warfarin therapy: The prevail trial. *J Am Coll Cardiol*. 2014;64:1-12
17. Friberg L, Rosenqvist M, Lip GY. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: The swedish atrial fibrillation cohort study. Eur. Heart J. 2012;33:1500-1510

28. Abbreviations and Definitions

28.1. *Definitions*

28.1.1. 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 haemorrhage 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, hypoglycaemia, 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 haemorrhage)

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.

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)

28.1.2. Classification of Bleeding events

In response to the need to develop, disseminate, and ultimately adopt standardized bleeding end-point definitions for subjects receiving antithrombotic therapy, the Bleeding Academic Research Consortium (BARC) convened in February 2010 at the US Food and Drug Administration (FDA) headquarters in White Oak, MD. BARC effort brought together representatives from academic research organizations, the FDA, the National Institutes of Health, and pharmaceutical and cardiovascular device manufacturers and independent physician thought leaders in the field of cardiovascular disease to develop consensus bleeding definitions that would be useful for cardiovascular clinical trials. Application of these definitions is recommended for both clinical trials and registries:

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 PINNACLE FLX trial, a BARC score of Type 3 a, b, c and 5 a and b will be considered a major bleed.