Post-Market Real World Outcomes in WATCHMAN FLX™ Pro Left Atrial Appendage Closure (LAAC) Device

HEAL-LAA

S2504

CLINICAL INVESTIGATION PLAN

National Clinical Trial (NCT) Identifier Number: NCT05809596

Sponsored By

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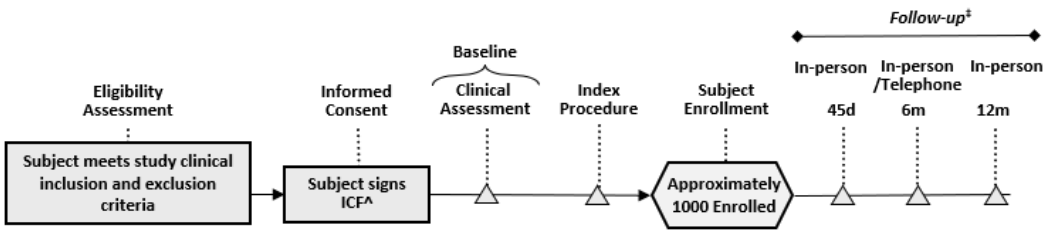
Revision Version	Protocol Date	Template number and version	Protocol Section Modified	Summary of Changes	Justification for Modification
A	17Mar2023	92120219_ Rev/Ver H	NA	NA	Initial Release
B	05May2023	92120219_ Rev/Ver H	Title Page	Addition of NCT Number	Alignment with FDAAA 801
			Throughout	Minor grammar & formatting	Clarity and readability
			2, 7.1	Increase number of subjects from 500 to 1000 and number of sites from 40 to 60	BSC decision to include additional Subsets
			2, 5, 6.2, 7.2, 9.1, 11.1, 11.2.3, 11.3.4, 24.2	Addition of Subsets	BSC decision to include Subset Analysis
			2, 5, 5.2, 7.2, 9.1, 24.2	Addition of Enrollment Guide	Allows for flexibility and management of Subset Enrollment
			2, 7.1	Updates to Study Duration	Adjusts due to trial expansion
			5.1	Updates to Device Polymer Details	Release of polymer coating details
			10.2.1, 11.3.6	Update to Enrollment Cap	Clarification of Cap Restrictions
			16.5	Update to Anticipated Benefits	To align with WATCHMAN regulatory documents

2. Protocol Synopsis

HEAL-LAA: Post-Market Real World Outcomes **in WATCHMAN FLX™ Pro Left Atrial Appendage Closure (LAAC) Device**	
Study Objective(s)	The primary objective of this study is to collect real-world outcomes data on WATCHMAN FLX™ Pro Left Atrial Appendage Closure (LAAC) Device in patients who are implanted with the WATCHMAN FLX Pro device in a commercial clinical setting.
Indication(s) for Use	As per the product Instructions for Use (IFU), WATCHMAN FLX™ Pro is intended 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 CHADS2 or CHA2DS2-VASc scores;* • *Are deemed by their physicians to be suitable for oral anticoagulation (OAC); and* • *Have an appropriate rationale to seek a non-pharmacologic alternative to OAC, taking into account the safety and effectiveness of the device compared to OAC*
(Commercial) Device/System applied as Standard of Care and sizes, if applicable	Commercially available WATCHMAN FLX™ Pro Left Atrial Appendage Closure Device sizes 20mm, 24mm, 27mm, 31mm, 35mm, and 40mm. **Note 1:** The WATCHMAN FLX™ Pro LAAC Device comes preloaded on the WATCHMAN FLX™ Pro Delivery Catheter. The preloaded delivery system is used in conjunction with a commercially available WATCHMAN® Access System (access sheath and dilator)*. *Specific WATCHMAN® Access System devices of interest for the treatment of non-valvular atrial fibrillation may be added as they become commercially available as defined in the Enrollment Guide(s).
Study Design	HEAL-LAA is a prospective, post-market, single-arm, multi-center trial evaluating safety and device success of the WATCHMAN FLX Pro device in subjects with non-valvular atrial fibrillation (AF). A patient is considered enrolled once an approved informed consent form has been signed, all clinical inclusion and no clinical exclusion criteria have been met, and the WATCHMAN FLX Pro device has been used for treatment and/or attempted to be used for treatment. Follow-up clinical assessment and imaging (Transesophageal Echocardiography (TEE)) will occur at 45 days (± 15 days) and 12 months (365 ± 30 days) following implant and will be assessed by an independent core laboratory. Clinical follow-up will be conducted at 45 days (± 15 days), 6 months (180 ± 30 days), and 12 months (365 ± 30 days) post index procedure. The study design is summarized below.

HEAL-LAA: Post-Market Real World Outcomes **in WATCHMAN FLX™ Pro Left Atrial Appendage Closure (LAAC) Device**	
	 ^ Subjects must sign the study ICF before any Non-Standard of Care / study-specific assessments can be carried out. If all baseline and procedure assessments are SOC, subject may sign after receiving the WATCHMAN FLX Pro device. ‡ Visits are in-person at 45 days & 12 months and in-person (preferred) or via telephone interview at 6 months. **HEAL-LAA Study Design Overview**
Planned Number of Subjects	Approximately 1000 subjects in whom a WATCHMAN FLX Pro device is implanted or attempted to be implanted will be enrolled. Four planned subset analyses will be conducted: • Primary Analysis Subset: Initial 500 enrolled subjects • Access System Subset • Diversity Subset • Full Enrollment Set (all enrolled subjects)
Planned Number of Sites /Countries	Up to 60 investigational centers in the United States.
Primary Efficacy Endpoint	The rate of leak >5 mm at 45-day post-implant TEE for the WATCHMAN FLX™ Pro Primary Analysis Subset is less than a performance goal (PG).
Primary Safety Endpoint	For the evaluable cohort, the composite rate of all-cause mortality, all stroke, systemic embolism, and major bleeding at 6 months for the WATCHMAN FLX™ Pro Primary Analysis Subset is less than a performance goal (PG).
Additional Endpoints	The individual components of the composite safety endpoints above will be reported separately in addition to the overall composites. The following will also be analyzed: • Cardiovascular/unknown death • Non-cardiovascular death • Disabling and Non-Disabling stroke • Ischemic stroke and Hemorrhagic stroke • International Society on Thrombosis and Haemostasis (ISTH) major and non-major clinically significant o Procedural bleeding & Non-procedural bleeding • Device related thrombus

HEAL-LAA: Post-Market Real World Outcomes in WATCHMAN FLX™ Pro Left Atrial Appendage Closure (LAAC) Device	
	• Pericardial effusion/tamponade requiring pericardiocentesis or surgery • Device implant success
Method of Assigning Patients to Treatment	The study is a single arm study. All patients enrolled in the study will receive/attempt to receive the WATCHMAN FLX Pro device.
Follow-up Schedule	Study procedures and follow-up visits will occur as follows: • WATCHMAN FLX Pro Implant procedure • 45-Day Follow-up to include TEE Imaging (45 ± 15 days post Implant) • 6-Month Follow-up (180 ± 30 days post Implant) • 12-Month Follow-up to include TEE Imaging (365 ± 30 days post Implant) Subjects who are enrolled but not implanted with a WATCHMAN FLX Pro device (Attempted implant only) will be followed for safety through 12 months after the initial attempted index procedure. Attempted implant subjects will not undergo protocol required imaging assessments. The study will be considered complete after all available enrolled subjects have finished the 12-month follow-up visit.
Study Duration	Enrollment is expected to be completed in approximately 6 months; therefore, the total study duration is estimated to be approximately 18 months.
Participant Duration	The study duration for each subject is expected to be approximately 12 months.
Inclusion Criteria	Inclusion criteria are listed below. IC1. Subject is of legal age to participate in the study. IC2. Subject has documented non-valvular atrial fibrillation (i.e., atrial fibrillation in the absence of moderate or greater mitral stenosis or a mechanical heart valve). IC3. Subject is clinically indicated for and is treated or attempted to be treated with a WATCHMAN FLX™ Pro device. IC4. Subject or legal representative is able to understand and willing to provide written informed consent to participate in the study. IC5. Subject is able and willing to return for required follow-up visits and examinations.

HEAL-LAA: Post-Market Real World Outcomes **in WATCHMAN FLX™ Pro Left Atrial Appendage Closure (LAAC) Device**	
Exclusion Criteria	Exclusion criteria are listed below. EC1. Subject has a documented life expectancy of less than 6 months. EC2. Subject is currently enrolled in another investigational study, except if the subject is participating in a mandatory governmental registry, or a purely observational registry with no associated treatment. EC3. Intracardiac thrombus is present. EC4. An atrial septal defect repair or closure device or a patent foramen ovale repair or closure device is present. EC5. The LAA anatomy will not accommodate a Closure Device. EC6. The patient has known hypersensitivity to any portion of the device material or the individual components such that the use of the WATCHMAN FLX™ Pro Device is contraindicated. EC7. Any of the customary contraindications for other percutaneous catheterization procedure (e.g., patient size too small to accommodate TEE probe or required catheters) or conditions (e.g., active infection, bleeding disorder) are present. EC8. There are contraindications to the use of anticoagulation therapy, aspirin, or $P2Y_{12}$ inhibitor. EC9. Subject is of childbearing potential and is, or plans to become, pregnant during the time of the study (method of assessment per study physician's discretion).
Adjunctive Pharmacologic Therapy	Subjects should be treated with one of the two IFU recommended pharmacologic regimens (OAC+ASA or DAPT) following WATCHMAN FLX Pro implantation.

Statistical Methods	
Analysis Sets	Analysis sets for the study are listed below. - Intention-To-Treat (ITT): This population includes all subjects who sign an Informed Consent Form, meet all clinical inclusion and no clinical exclusion criteria, and are implanted with the study device or attempted to be implanted with the study device. - Implanted: This population includes all subjects who sign an Informed Consent Form, meet all clinical inclusion and no clinical exclusion criteria,

	and who are implanted with the study device in the correct anatomical position.
Primary Efficacy Endpoint Statistical Hypothesis	The rate of leak >5 mm at 45-day post-implant TEE for the WATCHMAN FLX™ Pro Primary Analysis Subset is less than a performance goal (PG).
Statistical Test Method for the Primary Efficacy Endpoint	A one-sample z--test will be used to test the one-sided hypothesis that the primary efficacy endpoint rate for the WATCHMAN FLX Pro Primary Analysis Subset is less than a PG: H_0: $P_{WM\_Leak} \geq PG$ H_1: $P_{WM\_Leak} < PG$ where P_{WM_Leak} is the primary efficacy endpoint rate for the WATCHMAN FLX Pro Primary Analysis Subset and PG is the performance goal. The analysis set for the primary efficacy endpoint is the implanted analysis set from the Primary Analysis Subset.
Sample Size Parameters for the Primary Efficacy Endpoint	The sample size calculation for the primary efficacy endpoint of leaks is based on the following assumptions. • Expected rate for WATCHMAN FLX Pro < 2% (based on historic studies of FLXibility and PINNACLE FLX) • Testing margin = 3% • PG = 5% = expected rate (2%) + testing margin (3%) • 1-sided significance level (α) = 0.025 • Power (1 minus ß) > 85% • Number of evaluable subjects = 400 • Expected attrition rate = 20% • Primary Analysis Subset enrollment for the study = 500 subjects
Success Criteria for the Primary Efficacy Endpoint	If the *P* value from the one-sample z-test is <0.025, the rate of the primary efficacy endpoint for the WATCHMAN FLX Pro Primary Analysis Subset will be concluded to meet the PG. This corresponds to the one-sided upper 97.5% confidence bound on the observed rate of the primary efficacy endpoint being less than the PG.
Primary Safety Endpoint Statistical Hypothesis	For the evaluable cohort, the composite rate of all-cause mortality, all stroke, systemic embolism, and major bleeding at 6 months for the WATCHMAN FLX™ Pro Primary Analysis Subset is less than a performance goal (PG).

Statistical Test Method for the Primary Safety Endpoint	A one-sample z-test will be used to test the one-sided hypothesis that the 6-month primary safety endpoint rate for the WATCHMAN FLX Pro Primary Analysis Subset is less than a PG: H0: $P_{Safety} \geq PG$ H1: $P_{Safety} < PG$ where P_{Safety} is the primary safety endpoint rate for the WATCHMAN FLX Pro Primary Analysis Subset and PG is the performance goal. The analysis set for the primary safety endpoint is the ITT analysis set from the Primary Analysis Subset. This endpoint will also be analyzed for the implanted analysis set.
Sample Size Parameters for the Primary Safety Endpoint	The sample size calculation for the primary safety endpoint is based on the following assumptions. • Expected rate for WATCHMAN FLX Pro < 14% (based on historic data from FLXibility and PINNACLE FLX) • Testing margin = 7% (50% relative to the expected rate) • PG = 21% = expected rate (14%) + testing margin (7%) • 1-sided significance level (α) = 0.025 • Power (1 minus ß) > 95% • Number of evaluable subjects = 485 • Expected attrition rate = 3% • Primary Analysis Subset enrollment for the study = 500 subjects
Success Criteria for the Primary Safety Endpoint	If the P value from the one-sample z-test is <0.025, the rate of the primary safety endpoint for the WATCHMAN FLX Pro Primary Analysis Subset will be concluded to meet the PG. This corresponds to the one-sided upper 97.5% confidence bound on the observed rate of the primary safety endpoint being less than the PG.

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4. Introduction

4.1. *Background*

4.1.1. Atrial Fibrillation, Stroke, and the LAA

Atrial fibrillation (AF) is a common abnormal cardiac rhythm disturbance characterized by an irregular and often fast heart rhythm that results in uncoordinated contraction of the atria. The Global Burden of Disease project estimated approximately 46.3 million individuals worldwide were affected by AF/atrial flutter in 2016[1]. Its prevalence is age-dependent with a frequency exceeding 15% among individuals 80 years or older[2]. It is a major cause of sudden cardiovascular death and heart failure[3] and a major risk factor for ischemic stroke, with a poor prognosis regarding survival and residual disability[4-6]. The prevalence of AF is expected to rise over time due to the aging worldwide population[7-9].

Thrombus formation from stagnant blood flow in AF can lead to thromboembolism and stroke[10]. Reports have suggested that up to 90% of thrombi in the left atria of patients with nonvalvular atrial fibrillation (NVAF) are located in the left atrial appendage (LAA)[11-13]. The relative stasis that occurs in the LAA due to its narrow entrance orifice and interior trabeculations contributes to the observed thrombogenicity[14]. In patients with NVAF, initial stroke reduction therapy includes systemic oral anticoagulation (OAC) with warfarin and/or direct oral anticoagulants (DOACs) such as abigatran, rivaroxaban, apixaban, and edoxaban[15-18]. Given the observed long-term OAC limitations such as increased risk of major bleeding, drug interactions, and patient non-compliance[19,20], percutaneous LAA occlusion (LAAO) has been developed as a nonpharmacologic alternative[9,21].

4.1.2. WATCHMAN and LAAO

As noted above, percutaneous occlusion of the LAA is an alternative treatment for AF patients who are at high risk of stroke and not eligible for long-term anticoagulation therapy. The WATCHMAN™ Left Atrial Appendage Closure (LAAC) Device (WATCHMAN) is a permanent implantable device designed to seal off the LAA[22]. The implant includes a self-expanding nitinol frame structure with fixation anchors around the perimeter and a permeable polyester fabric (polyethylene terephthalate; PET) that covers the atrial-facing implant surface. The WATCHMAN device received Conformité Européenne (CE) mark in 2005 and United States Food and Drug Administration (FDA) approval in 2015.

The safety and efficacy of WATCHMAN was assessed in two multicenter randomized controlled trials (RCT) comparing outcomes with the device versus warfarin in high-stroke-risk NVAF patients intolerant of long-term anticoagulation. In PROTECT AF (N=463 WATCHMAN, N=244 warfarin), WATCHMAN was noninferior to warfarin in terms of the primary efficacy endpoint of stroke, cardiovascular/unexplained death, and systemic embolism (SE)[23]. In the subsequent PREVAIL RCT (N=269 WATCHMAN, N=138 warfarin), WATCHMAN was noninferior to chronic warfarin for the prevention of ischemic stroke and SE >7 days post procedure; the short-term complication rate that was observed in PROTECT AF was also reduced[24]. A meta-analysis of the two trials at 5-year follow-up showed similar rates for the combined stroke and SE endpoint but a significantly lower rate of hemorrhagic stroke, disabling stroke, non-procedural bleeding, and all-cause mortality with WATCHMAN[25].

The iterative WATCHMAN FLX™ LAAC Device was assessed in the prospective, nonrandomized, multicenter PINNACLE FLX study (N=400)[26]. The primary safety end point was the occurrence by hospital discharge or 7 days post procedure, whichever came later, of one of the following events: death, ischemic stroke, systemic embolism, device- or procedure-related events requiring cardiac surgery. The primary effectiveness end point was the incidence of effective LAA closure (peri-device flow ≤5 mm), as assessed by the echocardiography core laboratory at 12-month follow-up. The primary safety endpoint was met with a rate of 0.5% and a 1-sided 95% upper confidence interval (CI) of 1.6%, which was significantly below the performance goal of 4.2% (P<0.0001). The primary effectiveness endpoint was met with a rate of 100% and a 1-sided 95% lower CI of 99.1%, which met the performance goal of 97.0% (P<0.0001). WATCHMAN FLX received CE mark in 2019 and FDA approval in 2020[27].

The next generation WATCHMAN FLX™ Pro LAAC Device (WATCHMAN FLX Pro; see Section **0**) is anticipated to be approved by the FDA in 2023. This HEAL-LAA clinical trial will collect real-world data on the WATCHMAN FLX Pro device.

4.2. *Study Rationale*

The purpose of the HEAL-LAA study is to collect real-world data on the WATCHMAN FLX Pro LAAC device using TEE imaging and safety evaluations.

5. Commercial Device Description (part of Standard of Care)

As per the product Instructions for Use (IFU), the WATCHMAN FLX™ Pro Left Atrial Appendage Closure Device (Boston Scientific Corporation, Marlborough, MA, USA) is intended 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 CHADS2 or CHA2DS2-VASc scores;*
- *Are deemed by their physicians to be suitable for oral anticoagulation (OAC); and*
- *Have an appropriate rationale to seek a non-pharmacologic alternative to OAC, taking into account the safety and effectiveness of the device compared to OAC*

The commercially available WATCHMAN FLX Pro LAA Closure Device comes preloaded on the WATCHMAN FLX Pro Delivery Catheter (Section **5.1**). In the HEAL-LAA study, this preloaded delivery system may be used in conjunction with any version of the commercially available WATCHMAN® Access System to facilitate device placement in the LAA via femoral venous access and crossing of the inter-atrial septum into the left atrium.

The trial is intended to be a scalable platform where devices and/or patient subsets and analyses of interest can be added or discontinued without major revisions to the protocol. BSC devices for the treatment of atrial fibrillation beyond those specified may be added as they become commercially available. An Enrollment Guide(s) will be provided to sites in order to communicate which devices and/or patient subsets are eligible for enrollment or devices/patient subsets that are no longer eligible for enrollment. Eligible devices will include market-released devices wi. Enrollment may be closed when there are an adequate number of enrollments to effectively meet trial objectives for the device and/or patient subset. The sponsor reserves the right to close enrollment of a device and/or patient subset at a site level. Site-specific enrollment closure for a device and/or patient subset will be communicated in

writing to the individual impacted site. Updates to the Enrollment Guides may be made for different patient subsets and analyses of interest throughout the course of trial enrollment.

The study will only use commercial devices.

5.1. *Overview of WATCHMAN FLX Pro*

The commercially available WATCHMAN FLX Pro Delivery System has two main parts: a WATCHMAN FLX Pro LAA Closure Device implant and a delivery catheter for implant introduction and placement.

The delivery catheter (**Figure 5.1-1**) 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 implant (**Figure 5.1-1**) consists of a self-expanding nitinol frame structure with fixation anchors around the perimeter and a permeable polyester fabric (polyethylene terephthalate) that covers the atrial-facing implant surface. A polyvinylidene difluoride-hexafluoropropylene (PVDF-HFP) coating is applied on the finished implant (including the fabric) via a dip-coating process. The coating is designed to improve hemocompatibility of the device by lessening the severity of the acute foreign body response to the implant and encourage endothelialization. The Closure Device has three radiopaque (RO) markers at the plane of maximum diameter of the implant.

Table 5-1: WATCHMAN FLX Device Selection

shows the six available implant sizes ranging from 20 mm to 40 mm. Appropriate sizing is determined by LAA measurements using fluoroscopy and echocardiographic guidance.

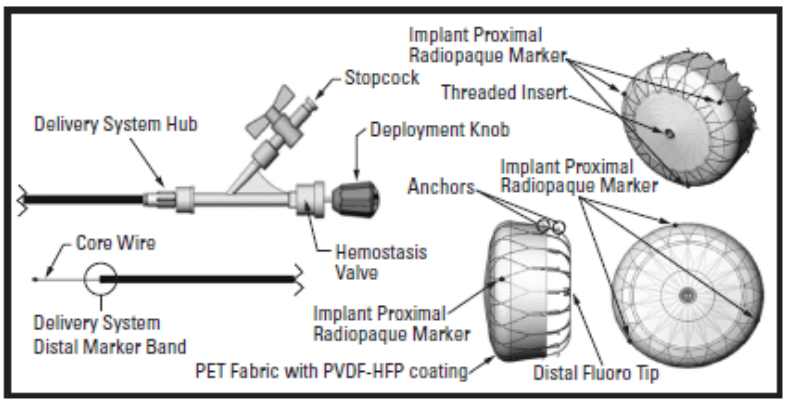

Figure 5.1-1: WATCHMAN FLX Pro Delivery System

Abbreviations: LAA=left atrial appendage; PET=polyethylene terephthalate; PVDF-HFP=polyvinylidene difluoride-hexafluoropropylene

Table 5-1: WATCHMAN FLX Device Selection

Maximum Left Atrial Appendage Ostium Width (mm)	Closure Device Size (mm)
14.0 – 18.0	20
16.8 – 21.6	24
18.9 – 24.3	27
21.7 – 27.9	31
24.5 – 31.5	35
28.0 – 36.0	40

The WATCHMAN FLX Pro LAA Closure Device implant is pre-loaded on the delivery catheter and is constrained within the catheter until deployment in the LAA. The implant is introduced percutaneously via femoral venous access using conventional catheterization techniques and is placed in the LAA after crossing the inter-atrial septum. It is deployed by loosening the valve on the delivery catheter and retracting the outer sheath. The implant can be partially recaptured and redeployed if initial placement is too distal. If the initial implant placement is too proximal, it can be fully recaptured and redeployed. The device is designed to be permanently implanted at or slightly distal to the ostium of the LAA to trap potential emboli before they exit the LAA. The placement procedure can be done under local or general anesthesia. More detailed product information can be found in the commercial IFU.

The WATCHMAN FLX Pro device offers additional features compared to the predicate WATCHMAN FLX™ Left Atrial Appendage Closure Device with Delivery System, as described in **Table 5-2**.

Table 5-2: WATCHMAN FLX Pro Additional Features

Feature	Purpose
Hemocompatible Coating	A PVDF-HFP coating applied on the finished implant (including the fabric) via a dip-coating process. The coating is designed to improve hemocompatibility of the device by lessening the severity of the acute foreign body response to the implant and encourage endothelialization.
Proximal Radiopaque (RO) markers	Proximal Radiopaque (RO) markers at the plane of maximum diameter of the implant to assist with visibility, deployment, and device positioning.
Deployment Knob Redesign	Improve user ergonomics and product identification
Wire Assembly Adjustments	To reduce the amount of air required to be removed from the Delivery System during preparation.
Additional 40 mm Size	Allow for treatment of a wider range of appendage sizes

5.2. *Required Medical Equipment*

Equipment needed for a WATCHMAN FLX Pro implant procedure are as follows:

- Venous introducer (optional)
- Standard transseptal access system
- 0.035 inch guidewire (exchange length extra support)
- 5F or 6F angiographic pigtail catheter
- Any commercially available WATCHMAN Access System (Access Sheath and Dilator)*

*Specific WATCHMAN® Access System devices of interest for the treatment of non-valvular atrial fibrillation may be added as they become commercially available as defined in the Enrollment Guide(s).

5.3. *Required Procedures & Medications*

A commercial training program has been established for the WATCHMAN FLX Pro Left Atrial Appendage Closure Device (Section **14.4.2**). Please see Section **10** for additional information on study methods.

6. Study Objectives and Endpoints

6.1. *Study Objectives*

The primary objective of this study is to collect real-world outcomes data on the WATCHMAN FLX Pro Left Atrial Appendage Closure (LAAC) Device in patients who are implanted with the WATCHMAN FLX Pro device in a commercial clinical setting.

6.2. *Study Endpoints*

Outcomes in HEAL-LAA will be assessed on an intention-to-treat (ITT) basis and an implanted basis. The ITT analysis set includes all subjects who sign an Informed Consent Form approved by the Institutional Review Board (IRB), meet all clinical inclusion and no clinical exclusion criteria, and the WATCHMAN FLX Pro device has been used for treatment and/or attempted to be used for treatment. The implanted analysis set includes ITT subjects who are implanted with the study device in the correct anatomical position (see full definitions within **Table 9-1** and **Table 24-2)**.

The trial endpoints are listed below. Measurements will be collected at baseline, pre-implant on the procedure day through discharge, and at 45 days, 6 months, and 12 months after the implant procedure, unless specified otherwise.

The **primary efficacy endpoint** is: The rate of leak >5 mm at 45-day post-implant TEE for the WATCHMAN FLX™ Pro Primary Analysis Subset is less than a performance goal (PG).

The **primary safety endpoint** is: For the evaluable cohort, the composite rate of all-cause mortality, all stroke, systemic embolism, and major bleeding at 6 months for the WATCHMAN FLX™ Pro Primary Analysis Subset is less than a performance goal (PG).

The Primary Analysis Subset consists of data from the initial 500 enrolled subjects.

Additional endpoints will include the following:

The individual components of the composite safety endpoints above will be reported separately in addition to the overall composites.

The following will also be analyzed:

- Death: Cardiovascular/unknown death and non-cardiovascular death
- Stroke: Disabling and non-disabling stroke; ischemic and hemorrhagic stroke
- Bleeding: International Society on Thrombosis and Haemostasis (ISTH) major and non-major clinically significant
  - Procedural bleeding (≤7 days post-procedure)
  - Non-procedural bleeding (>7 days post-procedure)

- Device related thrombus
- Pericardial effusion/tamponade requiring pericardiocentesis or surgery to treat
- Device implant success

See full definitions within **Table 24-2**.

Subset Analysis will be analysed per Section **11.3.4**.

7. Study Design

HEAL-LAA is a prospective, post-market, single-arm, multi-center trial evaluating safety and device success of the WATCHMAN FLX Pro closure device in subjects with non-valvular atrial fibrillation (AF).

7.1. *Scale and Duration*

Approximately 1000 subjects at up to 60 investigational centers in the United States will be enrolled in HEAL-LAA. Eligibility for the study is determined per standard of care. Any study specific testing to verify inclusion/exclusion criteria that is not considered Standard of Care at a given investigational center must be assessed after the ICF is signed. A patient is considered enrolled once an informed consent form has been signed, all clinical inclusion and no clinical exclusion criteria have been met, and the WATCHMAN FLX Pro device has been used for treatment and/or attempted to be used for treatment.

A subject who signs an ICF but does not meet clinical eligibility criteria and/or is not treated or attempted to be treated with a WATCHMAN FLX Pro device is considered a screen failure. Screen failure subjects should exit from the study immediately upon determining ineligibility.

Subjects who are enrolled but the attempted treatment with a WATCHMAN FLX Pro device was not successful will be followed for safety through 12 months after the initial attempted index procedure but will not undergo imaging assessments. See full “Attempted" definition within **Table 9-1.**

All subjects will be assessed at baseline and pre-implant on the procedure day through discharge, and at 45 days, 6 months, and 12 months post index procedure. Follow-up will include in-person clinical assessments at all time points except 6 months (in person [preferred] or by telephone). Follow-up imaging assessments will occur at 45 days and 12 months. Additional imaging may be done at 6 months per institution standard imaging practice.

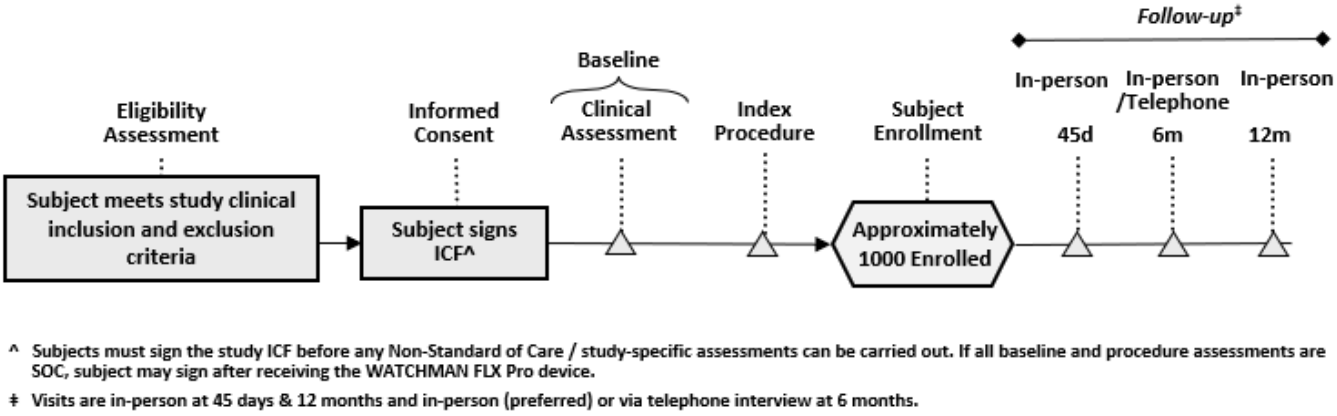

Figure 7.1-1: HEAL-LAA Study Design

Enrollment is expected to take 6 months. Therefore, the total study duration from first subject enrolled to last subject follow-up is estimated to be at least 18 months. The study duration for each subject is expected to be approximately 12 months.

The HEAL-LAA study will be registered at www.ClinicalTrials.gov prior to enrollment of the first subject (see Section **21.1**).

7.2. *Treatment Assignment*

HEAL-LAA is a post-market study. All subjects who meet all inclusion criteria and no exclusion criteria can be enrolled. A subject is considered enrolled in the study when the subject signs an ICF approved by the IRB, meet all inclusion criteria and no exclusion criteria, and are treated with or attempted to be treated with a WATCHMAN FLX Pro device. See Section **5.1** for a detailed description of the device and information on device sizes.

Additional patient subsets and/or analyses of interest may be included in the trial. An Enrollment Guide(s) will be provided to sites in order to communicate which patient subsets are eligible for enrollment and which subsets are no longer eligible for enrollment.

Subjects may meet more than one subset requirement and therefore may have their data analyzed in multiple subsets. Requirements for each subset will be outlined in the Enrollment Guide. Additional eligibility criteria outside of those listed within this protocol (Sections **8.2** and **8.3**) will not be introduced within the Enrollment Guide.

7.3. *Justification for the Study Design*

HEAL-LAA is an observational, post-market study designed to collect real world data on the WATCHMAN FLX Pro LAAC device to support further regulatory submissions. Device implantation will be done according to current indications and device labelling as described in the device IFU. Safety results and device success will be reported on all enrolled subjects. Enrolled subjects will be followed for up to 12 months post index procedure.

8. Subject Selection

8.1. *Study Population and Eligibility*

The intended population for the HEAL-LAA trial is real-world patients who are treated with the commercially available WATCHMAN FLX Pro device. Efforts will be made to include study centers with diverse patient populations in order to enroll populations previously not represented in LAAC trials.

Eligibility for this study is determined per standard of care. Any subject who meets all the inclusion criteria, does not meet any of the exclusion criteria, and who provides written informed consent may be considered for enrollment in the study (see **Note 1** below). The subjects selected for participation may be from the Investigator's general patient 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 below. All subjects will have unique identification numbers.

Note 1: Vulnerable subjects (see **Table 24-2** for the definition of vulnerable subject) will not be enrolled in the HEAL-LAA study.

8.2. *Inclusion Criteria*

Subjects who meet all of the following criteria (see **Table 8-1**) may be given consideration for inclusion in this clinical investigation, provided no exclusion criterion (see Section **8.3**) is met.

Table 8-1: Inclusion Criteria

Inclusion Criteria	IC1. Subject is of legal age to participate in the study. IC2. Subject has documented non-valvular atrial fibrillation (i.e., atrial fibrillation in the absence of moderate or greater mitral stenosis or a mechanical heart valve). IC3. Subject is clinically indicated for and is treated or attempted to be treated with a WATCHMAN FLX™ Pro device. IC4. Subject or legal representative is able to understand and willing to provide written informed consent to participate in the study. IC5. Subject is able and willing to return for required follow-up visits and examinations.

Abbreviation: IC=inclusion criterion

8.3. *Exclusion Criteria*

Subjects who meet any one of the following criteria (see **Table 8-2**) will be excluded from this clinical study. No vulnerable populations will be enrolled in this study.

Table 8-2: Exclusion Criteria

Exclusion Criteria	EC1. Subject has a documented life expectancy of less than 6 months. EC2. Subject is currently enrolled in another investigational study, except if the subject is participating in a mandatory governmental registry, or a purely observational registry with no associated treatment. EC3. Intracardiac thrombus is present. EC4. An atrial septal defect repair or closure device or a patent foramen ovale repair or closure device is present. EC5. The LAA anatomy will not accommodate a Closure Device. EC6. The patient has known hypersensitivity to any portion of the device material or the individual components such that the use of the WATCHMAN FLX™ Pro Device is contraindicated. EC7. Any of the customary contraindications for other percutaneous catheterization procedure (e.g., patient size too small to accommodate TEE probe or required catheters) or conditions (e.g., active infection, bleeding disorder) are present. EC8. There are contraindications to the use of anticoagulation therapy, aspirin, or $P2Y_{12}$ inhibitor. EC9. Subject is of childbearing potential and is, or plans to become, pregnant during the time of the study (method of assessment per study physician's discretion).

Abbreviations: EC=Exclusion Criteria; LAA=left atrial appendage; TEE=transesophageal echocardiography

9. Subject Accountability

9.1. *Point of Enrollment*

Subjects are considered enrolled in the study when the subject signs an ICF approved by the IRB, all clinical inclusion and no clinical exclusion criteria have been met, and the WATCHMAN FLX Pro device has been used for treatment and/or attempted to be used for treatment. Both Attempt and Implant subjects as defined in **Table 9-1** are considered enrolled subjects. A subject who is determined to not meet study specific clinical eligibility criteria after signing consent will be considered a screen failure (see **Table 9-1**) and will not count towards the enrollment ceiling.

An Enrollment Guide(s) will be provided to sites in order to communicate which devices and/or patient subsets are eligible for enrollment or devices/patient subsets that are no longer eligible for enrollment. Enrollment may be closed when there are an adequate number of enrollments to effectively meet trial objectives for the device and/or subset. The sponsor reserves the right to close enrollment of a device and/or subset at a site level.

9.2. *Withdrawal*

All subjects enrolled in the clinical study (including those withdrawn from the clinical study) shall be accounted for and documented. If a subject withdraws from the clinical investigation, the reason(s) shall be reported. Reasons for withdrawal include but are not limited to physician discretion, subject choice to withdraw consent, or death. Reasons for study exit will be captured in the secure electronic data capture (EDC) system. If such withdrawal is due to problems related to device safety or performance, the investigator shall ask for the subject's permission to follow his/her status/condition outside of the clinical study.

While all efforts will be made to minimize attrition, subjects may withdraw from the study at any time, with or without reason, and without prejudice to further treatment. Withdrawn subjects will not undergo any additional study follow-up, nor will they be replaced. The investigator may discontinue a subject from participation in the study if the investigator feels that the subject can no longer fully comply with the requirements of the study or if any of the study procedures are deemed potentially harmful to the subject. Data that have already been collected on withdrawn subjects will be retained and may be used for analysis unless local regulations apply. No new data will be collected after subject withdrawal.

All applicable case report forms up to the point of subject withdrawal and an "End of Study" form for the subject must be completed. If the withdrawal is due to investigator discretion, the investigator should follow-up with the subject per standard of care.

9.3. *Lost to Follow-Up (Missed Visits)*

All enrolled subjects will be followed for up to 12 months post-procedure.

Patients will not be considered lost to follow-up if he or she fails to be available for scheduled visits and is unable to be contacted by study center staff. The following actions will be taken if a subject fails to be available for a required study visit.

- The center will attempt to contact the subject and reschedule the missed visit and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain if the subject wishes to and/or should continue in the study
- A minimum of 3 attempts (i.e., 2 phone calls followed by a certified letter, or other traceable letter, if necessary) should be made to contact the patient or patient's next of kin for each missed follow-up visit and this information should be documented in the subject's medical record or study file.
- Should the subject continue to be unreachable through the 12-month visit, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

9.4. *Subject Status and Classification*

Table 9-1 describes subject status/classification and associated forms.

Table 9-1: Subject Status and Classification

Classification	Description
Screen Failure	A subject who signs an ICF but does not meet clinical eligibility criteria and/or is not treated or attempted to be treated with a WATCHMAN FLX Pro device is considered a screen failure. Screen failure subjects do not count towards the enrollment ceiling and will not be used for the primary analyses. Screen failure subjects should exit from the study immediately upon determining ineligibility. The original signed ICF must be maintained in the center's subject file.
Attempt	A subject who signs an ICF, meets eligibility criteria, and has had a WATCHMAN Access Sheath inserted to implant the device, but does not receive a WATCHMAN FLX Pro device will be classified as "Attempt." Subjects in which a WATCHMAN FLX Pro device is inserted into a different anatomical location/structure (not within the LAA) will also be classified as "Attempt." Attempt subjects will be followed for 12 months from the time of the implant attempt and adverse events will be collected. Attempt subjects will not undergo protocol required imaging at 45 days or 12 months. Attempt subjects are considered enrolled and therefore count towards the enrollment ceiling. Attempt subjects will be used for analyses of the ITT analyzed endpoints. The original signed ICF must be maintained in the center's study file and the following forms must be completed. • eCRFs in the Baseline and Implant folders • Follow-up Visit Form(s), except LAA imaging • Adverse Event forms and/or Device Deficiency forms for any reportable adverse event that occurs after signing the ICF • End of Study form for withdrawal The date of withdrawal should be indicated in the End of Study form as the point of subject withdrawal.
Implant	A subject who signs an ICF, meets eligibility criteria, and is implanted with the WATCHMAN FLX Pro device will be classified as "Implant." Implanted subjects are those where the device has been deployed and implanted in the correct anatomical position (LAA). These enrolled subjects are followed in accordance with the follow-up schedule and data will be included in all study analyses. All applicable case report forms per the protocol must be completed. The original signed ICF and any relevant documentation must be maintained in the center's study file.

Abbreviations: eCRF=electronic case report form; ICF=Informed Consent Form; LAA=left atrial appendage

9.5. *End-of-Study Definition*

This clinical study will be considered completed when subjects are no longer being examined or the last subject's last study visit as outlined in the data collection schedule (**Table 10-1** below) has occurred. All enrolled subjects will be evaluated clinically peri-procedural through discharge, and at 45 days, 6 months, and 12 months post index procedure (preferably all in-person visits).

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 ongoing. Events assessed as related to the device should be followed through resolution if possible and if consent has been provided by the subject for data collection on these events.

10. Study Methods

10.1. *Data Collection*

This section lists the data needed to fulfill the objectives of this clinical study.

The data collection schedule is provided in **Table 10-1**. Additional information, including recommended post-procedure medical therapy, is provided in Section **10.2** through Section **10.12**.

Table 10-1: Data Collection Schedule

Procedure/Assessment	**Baseline Assessment**[h]	**Index Procedure** (WATCHMAN FLX Pro)	**Follow-up Visits**		
			45-Days (±15 days) Follow-up & Imaging (Office)	**6-Months (±30 days) Follow-up** (Office or Telephone)	**12-Months (±30 days) Follow-up & Imaging** (Office)
Informed consent process (including informed consent signature date)	X	--	--	--	--
Demographics	X	--	--	--	--
Physical assessment	X	--	--	--	--
HAS-BLED & $CHAD_2DS_2$-VASc scores	X	--	--	--	--
Medical history	X	--	--	--	--
Pre-procedure LAA imaging (TEE/CT)[c]	O	--	--	--	--
Pregnancy Test[d]	X	--	--	--	--
Procedure and device information, procedure & discharge assessments	--	X	--	--	--
Procedural Imaging (TEE/ICE)[b]	--	X	--	--	--
Follow-up LAA imaging (TEE)[b]	--	--	X[a]	O	X[a]
Modified Rankin Scale[e]	X	X[g]	X[g]	X[g]	X[g]
Medication Regimen Review (anti-coagulation, anti-platelet, aspirin)	X	X	X	X	X
Adverse event assessment and device deficiency monitoring[f]	--	X	X	X	X

X = required; O = optional but recommended; -- = not required

[a] Implant subjects only (does not include Attempts). TEE imaging for core lab analysis is required at the 45-day and 12-month visits and must be submitted to the sponsor.

[b] All TEE, CT, and ICE images collected as part of the procedure and follow up visits (protocol defined, unscheduled, or SOC) through 12 months should be submitted for core lab analysis. Imaging collected as part of pre-procedure planning will not be submitted to the core lab. Collection of these images at the 6-month and unscheduled visits is not a protocol requirement. It is recommended that imaging be performed after a neurological event to screen for Device Related Thrombus. Image collection during the index procedure and at the 45 day and 12-month imaging visits must be collected by study personnel trained to the Imaging Manual.

[c] Pre-procedural planning imaging (TEE / CT) is recommended per the IFU if ICE will be used to guide the implant procedure.

[d] Required prior to implant for subjects of childbearing potential, who are pregnant or plans to become pregnant during the time of the study (method of assessment per investigator discretion.)

[e] mRS assessments should be performed by trained and certified study personnel (or Neurologist).

[f] Safety events will be monitored and reported to Boston Scientific Corporation per **Section 17.1**. Please refer to **Section 19.2** for a list of events to be adjudicated by the CEC through completion of a subject's participation in the study and **Table 17-1** for definitions of these events, which specify data required for CEC adjudication. Reporting of device deficiencies will follow applicable regional post-market safety surveillance requirements.

[g] mRS is to be conducted ONLY if there is a neurological event. Collection is required at the time of the event and 90d post-event per Section **10.9**.

[h] Some baseline assessments including Informed Consent may be collected after treatment with a WATCHMAN FLX Pro device per Section **10.3** & **10.4**.

10.2. *Study Candidate Screening*

Investigators are responsible for screening all subjects and selecting those who are appropriate for study inclusion as per the product IFU. No study-specified procedures or tests will be done prior to consent, though studies, tests, or procedures performed as part of the normal standard of care may be performed prior to consent.

10.2.1. Strategies for Recruitment and Retention

Subjects may be recruited through the Investigator's practice, referring physicians, and/or the use of recruitment tools. Potential subjects may be identified through an investigational center's database query (chart reviews) or as new or existing patients attend clinic visits. Any information disseminated to potential patients (e.g., advertisements, pamphlets, posters) must be approved by the investigational center's IRB prior to use.

Investigators should make efforts to screen and enroll diverse and previously underrepresented patient populations in LAAC trials, including women and minorities. Boston Scientific seeks to enroll diverse populations including representative proportions of relevant age, racial, and ethnic subgroups, which are consistent with the intended use population of the devices. Therefore, case report forms will collect data on age, race, and ethnicity. To ensure a diverse population is enrolled, BSC reserves the right to restrict enrollment to patients of diverse and previously underrepresented populations. Should enrollment restrictions be placed on sites, restrictions will be communicated via the Enrollment Guide(s).

Note: With a goal of achieving an unbiased estimate of treatment effect in the general population, Boston Scientific seeks to enroll a diverse population including representative proportions of relevant age, racial, and ethnic subgroups, which are consistent with the intended use population of the device. Case Report Forms will collect data on age, race and ethnicity in order to achieve this goal (https://www.fda.gov/media/98686/download)

Follow-up visits should be performed per local practice and every effort must be made by the site to retain study patients for the duration of the study and to collect patient data per the Data Collection Schedule in Section **10.1**.

10.3. *Informed Consent*

Subjects must sign the approved study ICF before any non-standard of care, study specific assessment can be assessed. If all baseline and procedure assessment/procedures are SOC, a subject may sign the ICF after receiving the WATCHMAN FLX Pro device. Subjects that have signed and dated the ICF, have met all clinical inclusion and no clinical exclusion criteria, and have been treated with or attempted to be treated with a WATCHMAN FLX Pro device are considered enrolled in the study. 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 Investigator/designee who has been trained on the protocol will explain the nature and scope of the study, the potential risks and benefits of participation, and will answer questions for the subject. Patients must be given ample time to review the ICF and have questions answered before signing.

10.4. *Baseline Assessments*

The following pre-procedure data should be collected within 30 days prior to the index procedure for all patients but will follow local standard of care practice. If mRS is not standard of care prior to the Index Procedure, it is to be collected by study personnel per Section **10.9.1**. Baseline assessments performed per Standard of Care outside of the 30-day window can be used and will not be a protocol deviation if no data within 30 days are available. Assessments indicated with an '*' are expected to be collected prior to implant.

- Confirmation of eligibility criteria
- Clinical assessments
  - Demographics, including age at time of consent, race, ethnicity, and sex
  - Medical, cardiac, and neurological history including cardiovascular diseases, AF type (paroxysmal/persistent/permanent) and time since AF diagnosis; prior history of ischemic stroke, hemorrhagic stroke and/or TIA; previous cardiac procedures; history of bleeding and location; and NSAID use
  - HAS-BLED, and CHA_2DS_2-VASc scores*
  - Physical assessment includes height and weight*
  - Current medication regimen review for the use of antiplatelet, aspirin, and anticoagulant medications
  - Modified Rankin Scale (mRS)*
  - Pregnancy test for Women Of Childbearing Potential, who are pregnant or plans to become pregnant during the time of the study (method of assessment per investigator discretion) *
- Imaging assessments
  - Pre-procedural imaging (TEE / CT) is recommended per the IFU if ICE will be used to guide the implant procedure. *

10.5. *Pre-procedure Medications*

Pre-procedure medications are listed below and should be recorded on the eCRFs.

- Single antiplatelet therapy (aspirin or $P2Y_{12}$ inhibitor) is recommended prior to device implantation. A loading dose should be administered the day before the implant procedure. Dosing should be per standard of care. The choice of loading dose medication is at the discretion of the treating physician.
- Anticoagulant therapy (e.g., unfractionated heparin) must be administered per local standard of care during the implant procedure.
- Prophylactic antibiotic therapy should be given according to local practice. The choice of antibiotic drug is left to the investigator's discretion.

10.6. *Index Procedure*

The preparation of the subject for the transcatheter procedure will be performed following standard techniques. Refer to the WATCHMAN FLX Pro LAA Closure Device IFU and the WATCHMAN® Access System IFU for detailed instructions regarding device use.

NOTE: If using a new to the market WATCHMAN Access System, it is recommended that the implanting physicians do not utilize the new access system until they have successfully implanted at least five (5) WATCHMAN FLX Pro devices with their standard access system.

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

The following information will be collected in the eCRF during the procedure. The study eCRFs identify the specific data points to be collected.

- Current medication regimen review for the use of antiplatelet, aspirin and anticoagulant medications.
- Adverse events experienced at implant procedure. Refer to Section **17** for detailed information on Safety reporting.
- Procedure related data including:
  - WATCHMAN FLX Pro Device usage information, including device size and compression post-implant
  - Access System(s) usage information
  - Transseptal Access System usage information
  - LAA imaging information (TEE/ICE): LAA size/shape, number of lobes in LAA, and location of lobes to ostium
  - Device release criteria measurements
  - Name of implanting physician
  - Duration of procedure and fluoroscopy
  - Procedural medications
  - Type of anesthesia
  - Device Deficiencies
- TEE / ICE images must be submitted for core lab analysis for independent analysis. Image collection during the index procedure must be collected by study personnel trained to the Imaging Manual.

10.7. *Discharge & Medication Regimen*

The subject may be discharged from the hospital when clinically stable, at the Investigator's discretion per local standard of care. Prior to discharge from the hospital, a safety event assessment must be done. This includes evaluation of any procedure-related adverse event (AE), serious adverse event (SAE), adverse device effect (ADE), serious adverse device effect (SADE), unanticipated serious adverse device effect (USADE), and any device deficiency. The study eCRFs identify the specific data points to be collected.

For subjects diagnosed with a neurological event (e.g., stroke, TIA), refer to section **10.9** for further assessments.

Antiplatelet therapy post index procedure is recommended to reduce the risk of thrombotic or thromboembolic complications if there are no contraindications to these medications. Subjects should be treated with one of the two IFU recommended pharmacologic regimens (OAC+ASA or DAPT) following WATCHMAN FLX Pro implantation. Extended therapy may be administered per physician choice.

Prior to discharge, clinical staff should review the study follow-up visit schedule with the subject to maximize follow-up compliance.

10.8. *Follow-up Visits*

All enrolled subjects will be evaluated at 45 days, 6 months, and 12 months post index procedure. Attempt subjects (see **Table 9-1**) will be followed for safety through 12 months after the initial attempted index procedure but will not undergo protocol required imaging assessments.

It is important that this schedule be maintained as closely as possible for all subjects. Boston Scientific Corporation (BSC) recognizes that subjects may not be able to return for all scheduled visits at precisely the date required, and therefore, a period of time in which each visit is allowed is indicated within Sections **10.8.1, 10.8.2,** and **10.8.3**. Required follow-up assessments, visits completed outside the follow-up windows, and visits not completed will be recorded as protocol deviations. Each follow-up visit must be performed by trained study personnel. Data from collected tests and images as well as medical assessments will be recorded in source documentation and captured in the eCRFs.

In the event that study personnel learn of a subject's hospitalization outside the study center, the center should make every effort to obtain copies of reports or results based on tests (e.g., echocardiogram) and/or procedures performed on the study subject.

10.8.1. 45-Day Follow-up (45 Days ±15 Days)

All enrolled subjects will be evaluated 45 days after the index procedure. The study eCRFs identify the specific data points to be collected as listed below.

- Complete safety event assessment (Section **17**), including any SAE, ADE, SADE, USADE, device deficiency, and any CEC event (Section **19.2**) regardless of seriousness and device relationship.
  - For subjects diagnosed with a neurological event (e.g., stroke, TIA), refer to Section **10.9** for further assessments.
- Current antithrombotic medication regimen. Dose changes, medication interruptions, and medication cessation must be documented
  - All antithrombotic medications should be administered in accordance with local standard of care and per one of the two IFU recommended pharmacologic regimens.
- LAA Imaging (as directed by the IFU): TEE is required at 45 days for all Implanted subjects and must be performed per the core lab guidelines by study personnel trained to the Imaging Manual, including assessment of device seal and device surface morphology (inclusive of tissue coverage) post implant procedure. Images must be sent to the core lab for independent analysis. Attempt subjects do not require LAA Imaging.

10.8.2. 6-Month Follow-up (180±30 Days)

All enrolled subjects will be evaluated 6 months after the index procedure. The study eCRFs identify the specific data points to be collected as listed below.

- Complete safety event assessment (Section **17**), including any SAE, ADE, SADE, USADE, device deficiency, and any CEC event (Section **19.2**) regardless of seriousness and device relationship.
  - For subjects diagnosed with a neurological event (e.g., stroke, TIA), refer to section **10.9** for further assessments.
- Current medication regimen for the use of antiplatelet, aspirin, and anticoagulants. Dose changes, medication interruptions, and medication cessation must be documented.
  - All antithrombotic medications should be administered in accordance with local standard of care and per one of the two IFU recommended pharmacologic regimens.
- TEE and/or CT is optional and/or based on SOC. However, if TEE and/or CT is performed for Implanted subjects, images should be sent to the core lab for independent analysis.
  - It is recommended that LAA imaging at the 6-month visit is conducted by staff trained to the Imaging Manual.

10.8.3. 12-Month Follow-up (365±30 Days)

All enrolled subjects will be evaluated 12 months after the index procedure. The study eCRFs identify the specific data points to be collected as listed below.

- Complete safety event assessment (Section **17**), including any SAE, ADE, SADE, USADE, device deficiency, and any CEC event (Section **19.2**) regardless of seriousness and device relationship.
  - For subjects diagnosed with a neurological event (e.g., stroke, TIA), refer to section **10.9** for further assessments.
- Current medication regimen for the use of antiplatelet, aspirin, and anticoagulants. Dose changes, medication interruptions, and medication cessation must be documented.
  - All antithrombotic medications should be administered in accordance with local standard of care and per one of the two IFU recommended pharmacologic regimens.
- LAA Imaging (as directed by the IFU): TEE is required at 12 months for all Implanted subjects and must be performed per the core lab guidelines by study personnel trained to the Imaging Manual, including assessment of device seal and device surface morphology (inclusive of tissue coverage) post implant procedure. Images must be sent to the core lab for independent analysis. Attempt subjects do not require LAA Imaging.

10.9. *Stroke or Systemic Embolism*

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

10.9.1. Stroke Scales and Cognitive Assessment

The Modified Rankin Scale (mRS) score assesses the severity of stroke disability and functional dependence of all subjects. The assessment should be performed by either a neurologist or personnel who have completed a certification for the mRS. The mRS must be collected for all subjects at Baseline. If mRS is not standard of care prior to the Index Procedure, it is to be collected by study personnel. Additionally, mRS must be collected following any stroke or TIA event and at 90 (± 15) days after a stroke or TIA event. The mRS collected following the stroke or TIA event, and at 90 (± 15) days after a stroke or TIA event, may be obtained by non-study personnel.

10.9.2. Stroke or Systemic Embolism and LAA Imaging

LAA imaging is strongly encouraged to help better ascertain the mechanism of the stroke or SE. This is not required. However, if imaging is performed, the imaging study should be sent to the core lab. It is recommended that LAA imaging performed to assess Stroke and/or Systemic Embolization is conducted by staff trained to the Imaging Manual. An optimal evaluation includes:

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

Should stroke, systemic embolism and/or LAA imaging be assessed outside of the index procedure, 45-day, 6-month, and 12-month visits, this data must be recorded within EDC via the unscheduled visit CRF and/or Adverse Event CRF.

10.10. *Device Thrombus*

The most accurate determination of whether thrombus has formed on the surface of the WATCHMAN FLX Pro Device is through LAA imaging evaluation (TEE or CT). In the case of thrombus on the atrial facing side of the device, anticoagulation therapy should be initiated per the investigator's standard of care. After the course of anticoagulation therapy, a repeat imaging evaluation should be performed to confirm the thrombus has resolved. This is not required. However, if imaging is collected, the imaging study should be sent to the core lab. It is recommended that LAA imaging performed to assess device thrombus is conducted by staff trained to the Imaging Manual. Cessation of anticoagulation therapy after this timepoint is at the discretion of the investigator.

Any identification of device thrombus must be reported on an adverse event case report form (CRF). A copy of all LAA imaging performed for evaluation of potential thrombus should be sent to the Core Lab, and a copy maintained in the subject's records.

Should device thrombus and/or LAA imaging be assessed outside of the index procedure, 45-day, 6-month, and 12-month visits, this data must be recorded within EDC via the unscheduled visit CRF and/or Adverse Event CRF.

10.11. *Study Completion*

All enrolled subjects will be followed for the duration of 12 months post procedure. A subject's participation in the study will be considered complete after the 12-month follow-up visit.

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 and Adverse Event form to resolve/close any AEs or deem chronic).

10.12. *Source Documents*

It is preferable that original source documents, when available, are maintained at the investigative center. In lieu of original source documents, certified copies are required to be maintained. A certified copy is a copy (irrespective of the type of media used) of the original record that has been verified (i.e., by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original. Source documentation includes but is not limited to those items noted in **Table 10-2**. Source documentation provided to the Sponsor for assessment/adjudication will be deidentified per local law and regulations.

Table 10-2: Source Documentation Requirements

Requirement	Disposition
Printed, optical, or electronic document containing source data. Examples include but are not limited to: hospital records; laboratory notes; device accountability records; photographic negatives; radiographs; records kept at the investigation center, at the laboratories and at the medico-technical departments involved in the clinical investigation.	Retain at center

Note 1: Please see **Table 24-2** for definitions of "source data" and "source document."

11. Statistical Considerations

11.1. *Endpoints*

11.1.1. Primary Efficacy Endpoints

The primary efficacy endpoint is that the rate of leak >5 mm at 45-day post-implant TEE for the WATCHMAN FLX™ Pro Primary Analysis Subset is less than a performance goal (PG).

11.1.1.1. Statistical Hypotheses for the Primary Efficacy Endpoint

A one-sample z-test will be used to test the one-sided hypothesis that the primary efficacy endpoint rate for WATCHMAN FLX Pro Primary Analysis Subset is less than a PG:

H_0: $P_{WM\_Leak} \geq PG$

H_1: $P_{WM\_Leak} < PG$

where P_{WM_Leak} is the primary efficacy endpoint rate for the WATCHMAN FLX Pro Primary Analysis Subset and PG is the performance goal.

The analysis set for the primary efficacy endpoint is the implanted analysis set from the Primary Analysis Subset. Core Lab data will be used for this analysis.

11.1.1.2. Sample Size

The sample size calculation for the primary efficacy endpoint of leaks is based on the following assumptions.

- Expected rate for WATCHMAN FLX Pro < 2% (based on historic studies of FLXibility and PINNACLE FLX)
- Testing margin = 3%
- PG = 5% = expected rate (2%) + testing margin (3%)
- 1-sided significance level (α) = 0.025
- Power (1 minus ß) > 85%
- Number of evaluable subjects = 400
- Expected attrition rate = 20%

Primary Analysis Subset enrollment for the study = 500 subjects.

If the *P* value from the one-sample z-test is <0.025, the rate of the primary efficacy endpoint for the WATCHMAN FLX Pro Primary Analysis Subset will be concluded to meet the PG. This corresponds to the one-sided upper 97.5% confidence bound on the observed rate of the primary efficacy endpoint being less than the PG.

11.1.2. Primary Safety Endpoint

The primary safety endpoint is the composite rate of all-cause mortality, all stroke, systemic embolization, and major bleeding events evaluated at 6 months after the implant procedure for the WATCHMAN FLX™ Pro Primary Analysis Subset.

11.1.2.1. Statistical Hypotheses for the Primary Safety Endpoint

The statistical hypothesis is that the rate of the primary safety endpoint (composite of all-cause mortality, all stroke, systemic embolization, and major bleeding events evaluated at 6 months after the implant procedure for the WATCHMAN FLX™ Pro device Primary Analysis Subset) is less than a performance goal (PG).

The primary safety endpoint is expressed as the proportion of Primary Analysis Subset subjects who experience mortality, stroke, systemic embolization, and major bleeding events within 6 months after the index procedure among all subjects who either experience mortality/stroke/systemic embolization/major bleeding complications within 6 months after the index procedure or are followed for at least 150 days after the index procedure.
The null and alternative hypotheses for the primary safety endpoint are as follows:

H_0: $P_{Safety} \geq PG$

H_1: $P_{Safety} < PG$

where P_{Safety} is the primary safety endpoint rate for the WATCHMAN FLX Pro Primary Analysis Subset and PG is the performance goal.

The analysis set for the primary safety endpoint is the ITT analysis set from the Primary Analysis Subset. This endpoint will also be analyzed for the implanted analysis set.

A one sample z test will be used to test the one-sided hypothesis of the PG for the WATCHMAN FLX Pro device. If the *P* value from the z test is <0.025, the rate of the primary safety endpoint for the WATCHMAN FLX Pro Primary Analysis Subset will be concluded to be less than the PG. This corresponds to the one-sided upper 97.5% confidence bound on the observed rate of the primary safety endpoint at 6 months being less than the PG.

11.1.2.2. Sample Size

The sample size calculation for the primary safety endpoint is based on the following assumptions.

- Expected rate for WATCHMAN FLX Pro < 14% (based on historic data from FLXibility and PINNACLE FLX)
- Testing margin = 7% (50% relative to the expected rate)
- PG = 21% = expected rate (14%) + testing margin (7%)
- 1-sided significance level (α) = 0.025
- Power (1 minus ß) > 95%
- Number of evaluable subjects = 485
- Expected attrition rate = 3%

Primary Analysis Subset enrollment for the study = 500 subjects

11.1.2.3. Statistical Methods

All enrolled subjects will be eligible for evaluation. Any events or hospitalizations occurring after the index procedure should be entered in the electronic data capture system. Events with onset date starting from the time of the index procedure will be included in the primary endpoint analysis.

Handling of dropouts and missing data will depend on their frequency and the nature of the outcome measure. Sensitivity analyses (e.g., tipping-point analysis) will be performed to assess the impact of subjects with inadequate follow-up (i.e., missing data) on the primary endpoint and to assess the robustness of the conclusion of the primary analysis. Statistical models that account for censored data will be employed in appropriate circumstances (e.g., for time-to-event outcomes). Suspected invalid data will be queried and corrected in the database prior to statistical analysis. Additional information may be found in the Statistical Analysis Plan.

11.2. *General Statistical Methods*

All statistical analyses will be performed using the SAS System software, version 9.2 or later (Copyright© 2000 SAS Institute Inc., SAS Campus Drive, Cary, North Carolina 27513, USA. All rights reserved).

All statistical analyses will be conducted according to applicable Standard Operating Procedures, Work Instructions, and the study-specific Statistical Analysis Plan.

11.2.1. Analysis Sets

Analysis sets for the study are listed below.

- Intention-To-Treat (ITT): This population includes all subjects who sign an Informed Consent Form, meet all clinical inclusion and no clinical exclusion criteria, and the WATCHMAN FLX Pro device has been used for treatment and/or attempted to be used for treatment (Implant & Attempt subjects).
- Implanted: This population includes all subjects who sign an Informed Consent Form, meet all clinical inclusion and no clinical exclusion criteria, and who are implanted with the study device in the correct anatomical position (Implant subjects).

11.2.2. Control of Systematic Error/Bias

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

To control for inter-observer variability, data from an independent core laboratory (see Section **12.4**) will be used for analysis at pre-specified time points. An independent CEC (see Section **19.2**) will adjudicate study endpoint related clinical events.

11.2.3. Number of Subjects per Investigative Site

To avoid any site effect and bias, no site will be authorized to implant or attempt more than 15% of the first 500 enrolled subjects (n = 75) per this protocol without prior approval from the sponsor. Sites that have reached the general enrollment cap may enroll additional subjects within the Diversity Subset. Enrollment cap waivers may be given for Access System Subset enrollment per the Enrollment Guide.

11.3. *Data Analyses*

Baseline and outcome variables will be summarized using descriptive statistics for continuous variables (mean, standard deviation, number of observations, minimum and maximum) and discrete variables (percentage and count/sample).

11.3.1. Additional Endpoints/Measurements

Additional endpoints not driven by statistical hypotheses are listed in Section **6.2**.

11.3.2. Interim Analyses

No formal interim analysis.

11.3.3. Subgroup Analyses

The following subgroups will be analyzed for the Primary Endpoints within the study:

- Sex (Female vs. Male)
- Age at time of consent (< 75 years vs. ≥ 75 years)
- Stroke risk (CHA_2DS_2-VASc Score)
- Bleeding risk (HAS-BLED Score)
- Race/ethnicity

11.3.4. Subset Analyses

The following subset will be analyzed for the Primary Endpoints and the Additional Endpoints within the study:

- Primary Analysis Subset

The Primary Analysis Subset consists of data from the initial 500 enrolled subjects.

Note: The hypothesis tests (PGs) are only based on the Primary Analysis Subset.

The following subsets will be analyzed per the Statistical Analysis Plan:

- Access System Subset
- Diversity Subset
- Full Enrollment Set (all enrolled subjects)

Note: All subset analysis as outlined within the Statistical Analysis Plan will be reported within the final clinical study report.

Subjects may meet more than one subset requirement and therefore may have their data analyzed in multiple subsets. Requirements for each subset will be outlined in the Enrollment Guide.

11.3.5. Multivariable Analyses

Univariate and multivariate analyses will be performed to assess the effect of potential predictors on the primary endpoint, as described in the statistical analysis plan.

11.3.6. Other Analyses

Exploratory univariate and multivariate analyses will be performed to assess the effect of potential predictors on the primary safety endpoint plus additional safety endpoints as described in the statistical analysis plan.
Additional statistical methods will be specified in the statistical analysis plan if applicable (such as: chi-square or t-test for comparison between subgroups).

11.3.7. Changes to Planned Analyses

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

12. Data Management

12.1. *Data Collection, Processing, and Review*

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

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

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

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

All access to the clinical database will be changed to “Read only” after all data is either “Hard Locked” or “Entry Locked”. Once acceptance of the final report or finalization of publications (as applicable) is

received, final database storage and archiving activities can begin. Once all of the closeout activities are completed a request to IT is submitted to have the database "Decommissioned" and all database access revoked.

12.2. *Data Retention*

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

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

12.3. *Technical Source Forms*

A Technical Source Form (TSF) may be developed by the investigational site to capture protocol required data elements that are not duplicated in any other source documents. This form is to be used by the study sites as a source document. The TSF will be reviewed and signed for approval by the Principal Investigator or his/her designee at the end of each procedure.

12.4. *Core Laboratories*

An independent core laboratory will be utilized to review LAA imaging collected starting at the Index Procedure and throughout the duration of the study. All interpretations of LAA imaging for purposes of subject care will be conducted by each site's investigator and/or imaging specialist. The Core Lab will not be utilized as a means of reference for subject management decisions.

LAA imaging will be collected by each study site according to the Imaging Manual and submitted to the Core Lab for review. The Core Lab will provide the sponsor with summary of results for reporting purposes. Training and adherence to the imaging manual is required for image collection at the Index Procedure and at the 45-day and 12-month TEE Imaging Assessments. It is recommended to follow the Imaging Manual for all other images collected and submitted to the Core Lab for analysis.

These analyses will minimize bias and inconsistencies by providing an independent interpretation of all measurements using standard techniques.

13. Deviations

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

later than 5 working days after the emergency occurred, or per prevailing local requirements, if sooner than 5 working days.

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

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

The sponsor will not approve protocol waivers.

14. Compliance

14.1. *Statement of Compliance*

This clinical investigation is financed by the study sponsor. Before the investigational site can be "Authorized to Enroll," the investigational site must enter into a Clinical Study Agreement with the sponsor that details the financing of the study as well as the rights and obligations of the investigational site and the investigator. This study will be conducted in accordance 21 CFR part 56, part 50, part 54 and part 812, EN ISO 14155, relevant parts of the ICH Guidelines for Good Clinical Practice, ethical principles that have their origins in the Declaration of Helsinki, and applicable individual country laws and regulations. The study shall not begin until the required approval/favorable opinion from the IRB has been obtained. The trial will not begin enrollment until the WATCHMAN FLX Pro device has received regulatory authority device approval. Also, the study shall not begin prior to issuance of the site Authorization to Enroll, as provided by the sponsor. Any additional requirements imposed by the IRB shall be followed, if appropriate.

14.2. *Investigator Responsibilities*

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

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

- Prior to beginning the study, sign the Clinical Study Agreement and comply with the Investigator responsibilities as described in such Agreement.
- Provide his/her qualifications and experience to assume responsibility for the proper conduct of the study and that of key members of the site team through up-to-date curriculum vitae or other relevant documentation and disclose potential conflicts of interest, including financial, that may interfere with the conduct of the clinical study or interpretation of results.

- Complete training requirements associated with the WATCHMAN FLX™ Pro Left Atrial Appendage Closure Device.
- Make no changes in or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency; document and explain any deviation from the approved protocol that occurred during the course of the clinical investigation.
- Create and maintain source documents throughout the clinical study and ensure their availability with direct access during monitoring visits or audits; ensure that all clinical-investigation-related records are retained per requirements.
- Ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.
- Record, report, and assess (seriousness and relationship to the device/procedure) every adverse event as applicable per the protocol and observed device deficiency.
- Report to sponsor, per the protocol requirements, all reportable events.
- Report to the IRB and regulatory authorities any SAEs and device deficiencies that could have led to a SADE and potential/USADE or UADE, if required by applicable laws or regulations or this protocol or by the IRB, and supply BSC with any additional requested information related to the safety reporting of a particular event.
- Allow the sponsor to perform monitoring and auditing activities and be accessible to the clinical research monitor or auditor and respond to questions during monitoring visits or audit(s).
- Allow and support regulatory authorities and the IRB when performing auditing activities.
- Ensure that informed consent is obtained in accordance with applicable laws, this protocol and local IRB requirements.
- Provide adequate medical care to a subject during and after a subject's participation in a clinical study in the case of adverse events, as described in the Informed Consent Form (ICF).
- Inform the subject of the nature and possible cause of any adverse events experienced.
- As applicable, provide the subject with necessary instructions on proper use, handling, storage, and return of the device when it is used/operated by the subject.
- Inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required.
- Provide the subject with well-defined procedures for possible emergency situations related to the clinical study and make the necessary arrangements for emergency treatment.
- Ensure that clinical medical records are clearly marked to indicate that the subject is enrolled in this clinical study.
- Ensure that, if appropriate, subjects enrolled in the clinical investigation are provided with some means of showing their participation in the clinical investigation, together with identification and compliance information for concomitant treatment measures (contact address and telephone numbers shall be provided).

- Inform, with the subject's approval or when required by national regulations, the subject's personal physician about the subject's participation in the clinical investigation.
- Make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from clinical investigation while fully respecting the subject's rights.
- Ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation.

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

14.2.1. Delegation of Responsibility

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

14.3. *Institutional Review Board*

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

A copy of the written IRB approval of the protocol (or permission to conduct the study) and ICF, must be received by the sponsor before recruitment of subjects into the study. Prior approval must also be obtained for other materials related to subject recruitment or which will be provided to the subject.

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

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

14.4. *Sponsor Responsibilities*

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

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

14.4.1. Role of Boston Scientific Representatives

Boston Scientific Corporation personnel (including field clinical engineers and specialists) who are trained in the use of the WATCHMAN FLX™ Pro Left Atrial Appendage Closure Device will provide training and technical support to the investigator and other health care personnel (collectively HCP) as needed during implantation of the WATCHMAN FLX Pro device. Boston Scientific Corporation has established a structured training program for the physicians and staff who will be involved in the peri-procedural care of subjects selected to receive the WATCHMAN FLX Pro device. Support may include HCP training (Section **14.4.2**), addressing HCP questions, or providing clarifications to HCPs concerning the operation of BSC equipment/devices.

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

- Commercial WATCHMAN Clinical Specialists: Provide technical expertise for the device that you will receive or, for the device testing that will be conducted as per the commercial process
- Commercial WATCHMAN Clinical Specialists: Be present at the procedure, follow-up visits, or other study related testing at your doctor's request as per the commercial process
- Clinical Trial Representatives: Review of collected data and study documentation for completeness and accuracy, relevant to protocol compliance.

Boston Scientific personnel will not do the following.

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

14.4.2. Training

Boston Scientific Corporation has established a structured training program for the physicians and staff who will be involved in the peri-procedural care of subjects treated with the WATCHMAN FLX Pro Left Atrial Appendage Closure Device. This commercial training program is designed to provide the physicians and staff with the information and experience necessary to control user-associated risks when the device is used in accordance with the IFU.

14.5. *Insurance*

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

15. Monitoring

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

A risk-based monitoring approach will be utilized. The specific details of the risk-based monitoring approach will be detailed in the monitoring plan and the Integrated Quality Risk Management Plan (IQRMP). Actively enrolling sites will be monitored as detailed in both the monitoring plan and the IQRMP.

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

16. Potential Risks and Benefits

16.1. *Instructions for Use*

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

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

Risks associated with the use of a left atrial appendage closure device or implantation procedure and with the WATCHMAN FLX Pro Left Atrial Appendage Closure Device are listed in the IFU and in the ICF. There are no incremental risks associated with participation in this clinical study.

Patients who take part in this study are subject to risks that are similar to those shared by all patients who receive the commercially available WATCHMAN FLX™ Pro Device and antithrombotic medication outside of this study.

Treatment with a WATCHMAN FLX Pro Left Atrial Appendage Closure Device has not been studied in pregnant women. There may be additional risks to a pregnant woman (or to the embryo or fetus if the subject is pregnant or becomes pregnant or are nursing an infant) which are unknown at this time.

TEE imaging is required to be completed at the 45-day and 12-month imaging visits. This imaging is required per the IFU. Potential risks associated with the TEE imaging procedure include:

- nausea
- esophageal damage, discomfort, or bleeding
    - in rare instances, damage to the trachea due to intubation is possible

16.3. *Possible Interactions with Concomitant Medical Treatments*

Please see Section **10.7** for suggested medications, which constitute standard of care for use of a left atrial appendage closure device. Information regarding risks associated with use of antiplatelet therapy or oral anticoagulants should be referenced with the medications. Patients who take part in this study are subject to risks that are similar to those shared by all patients who receive the commercially available antithrombotic medication outside of this study.

16.4. *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.

Data will be monitored as they are submitted to BSC. Qualified employees of BSC, or a designee under contract, will conduct monitoring visits at the initiation of the study and at interim intervals described in the monitoring plan throughout the course of the study to evaluate protocol compliance and determine if there are any issues that could affect the safety or welfare of any subject in the study. A dynamic safety review process including CEC (Section **19.2)** adjudication of specified events will support risk mitigation.

16.5. *Anticipated Benefits*

The clinical benefit of the WATCHMAN FLX Pro LAA Closure Device is to decrease the risk of stroke by preventing thrombus embolization from the left atrial appendage and decrease the risk of major bleeding events by reducing the need for long-term blood thinners in patients with non-valvular atrial fibrillation.

There may also be 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.

17. Safety Reporting

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

For enrolled subjects, it is the responsibility of the investigator to assess and report to BSC any event which occurs from the beginning of the Index Procedure through 12-month follow-up visit for all subjects including any of following categories:

- All Serious Adverse Events (SAE) regardless of cause – see **Note 1** below
- Adverse Events (AE) related to the WATCHMAN FLX Pro device and/or WATCHMAN FLX Pro implant procedure
- Unanticipated Adverse Device Effects (UADE) / Unanticipated Serious Adverse Device Effects (USADE)
- Adverse Event where systemic embolism is suspected and/or confirmed, regardless of relationship to the WATCHMAN FLX Pro device
- All bleeding events regardless of relationship to the WATCHMAN FLX Pro device
- All strokes (regardless of cause) and transient ischemic attacks (TIAs) regardless of relationship to the WATCHMAN FLX Pro device
- New findings/updates in relation to already reported events
- Device Deficiency

Note 1: Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without serious deterioration in health, is not considered a serious adverse event. Changes to the planned date of procedure/hospitalization are permitted and will not trigger event reporting.

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

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

Any reportable event, experienced by the study subject after informed consent and once considered enrolled in the study (as defined in Section **9.1**), whether prior to, during or subsequent to the study procedure, must be recorded in the eCRF.

Underlying diseases and chronic conditions are not reported as AEs unless there is an increase in severity or frequency during the course of the investigation. Death should not be recorded as an AE but should only be reflected as an outcome of one (1) specific SAE (see **Table 17-1** for AE definitions).

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

17.2. *Definitions and Classification*

Adverse event definitions are provided in **Table 17-1**. Administrative edits were made on the safety definitions from applicable regulations and guidance including (but not limited to) 21 CFR Part 812, ISO 14155 and EU MDR 2017/745/MDCG 2020-10/1 Guidance on Safety Reporting in Clinical Investigations for clarification purposes.

Table 17-1: Safety Definitions

Term	Definition
Adverse Event (AE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the study medical device and whether anticipated or unanticipated. **NOTE 1**: This includes events related to the study medical device or comparator. **NOTE 2**: This definition includes events related to the procedures involved. **NOTE 3**: For users or other persons, this definition is restricted to events related to the study medical device.
Adverse Device Effect (ADE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	Adverse event related to the use of the study medical device **NOTE 1**: This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the study medical device. **NOTE 2**: This definition includes any event resulting from use error or from intentional misuse of the study medical device. **NOTE 3**: This includes 'comparator' if the comparator is a medical device.
Serious Adverse Event (SAE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	Adverse event that led to any of the following: a) death, b) serious deterioration in the health of the subject, users or other persons as defined by either: 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, including chronic diseases, or 3) in-patient hospitalization or prolongation of existing hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function c) fetal distress, fetal death, or a congenital abnormality or birth defect including physical or mental impairment. **NOTE 1:** Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without a serious deterioration in health, is not considered a serious adverse event. Changes to the planned date of procedure/hospitalization are permitted and will not trigger event reporting.

Table 17-1: Safety Definitions

Term	Definition
Serious Adverse Device Effect (SADE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated Adverse Device Effect (UADE) *Ref: 21 CFR Part 812*	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.
Unanticipated Serious Adverse Device Effect (USADE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current risk assessment. **NOTE 1**: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk assessment.
Serious Health Threat *Ref: ISO 14155*	Signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons. **NOTE 1**: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.
Device Deficiency *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	An inadequacy of a medical device related to its identity, quality, durability, reliability, usability, safety or performance. **NOTE 1**: Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling. **NOTE 2**: This definition includes device deficiencies related to the device under study.
The following definitions will be used for defining hospitalization or prolongation of hospitalization for SAE classification purposes:	
Hospitalizations	Hospitalization does not include: • emergency room visit that does not result in in-patient admission Note: although an emergency room visit does not itself meet the definition for hospitalization, it may meet other serious criteria (e.g., medical or surgical intervention to prevent permanent impairment or damage) • elective and pre-planned treatment/surgery for a pre-existing condition that is documented in the subject's record at the time of consent/enrollment • admission for social reasons and/or respite care in the absence of any deterioration in the subject's general condition (e.g., subject is homeless, caregiver relief) • pre-planned, protocol-specified admission related to the clinical study (e.g., procedure required by protocol)
Prolongation of hospitalization	In-patient admission to the hospital that is prolonged beyond the expected standard duration for the condition under treatment. Note: new adverse events occurring during the hospitalization are evaluated to determine if they prolonged hospitalization or meet another SAE criteria.

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

The Investigator must assess the relationship of the reportable AE to the study device(s), and/or implant procedure. See criteria in **Table 17-2Error! Reference source not found.**

Table 17-2: Criteria for Assessing Relationship of Study Device(s) or Procedure to Adverse Event

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

17.4. *Investigator Reporting Requirements*

The communication requirements for reporting to BSC are as shown in **Table 17-3**.

Table 17-3: Investigator Reporting Requirements

Event Classification	**Communication Method**	**Communication Timeline post-market studies*** (*EU MDR 2017/745, MDCG 2020-10/1*MEDDEV 2.12/1: GUIDELINES ON A MEDICAL DEVICE VIGILANCE SYSTEM)
Unanticipated Adverse Device Effect / Unanticipated Serious Adverse Device Effect	Complete AE eCRF page with all available new and updated information.	• Within 1 business day of first becoming aware of the event. • Terminating at the end of the study.
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• Upon request of sponsor.
Serious Adverse Event	Complete AE eCRF page with all available new and updated information.	• Within 10 calendar days after becoming aware of the event or as per local/regional regulations. • Reporting required through the end of the study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• When documentation is available • Upon request of sponsor
Serious Adverse Device Effects	Complete AE eCRF page with all available new and updated information.	• Within 3 calendar days of first becoming aware of the event or as per local/regional regulations. • Reporting required through the end of the study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• When documentation is available • Upon request of sponsor
Device Deficiencies (including but not limited to malfunctions, use errors, and inadequacy in information supplied by the manufacturer, including labelling) Note: Any Device Deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, circumstances had been less fortunate is considered a reportable event.	Complete applicable CRF fields/forms with all available new and updated information.	• Within 3 calendar days of first becoming aware of the event. • Reporting required through the end of the study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• Upon request of sponsor

Event Classification	**Communication Method**	**Communication Timeline post-market studies*** (*EU MDR 2017/745, MDCG 2020-10/1*MEDDEV 2.12/1: GUIDELINES ON A MEDICAL DEVICE VIGILANCE SYSTEM)
Adverse Event including Adverse Device Effects	Complete AE eCRF page, which contains such information as date of AE, treatment of AE resolution, assessment of seriousness and relationship to the device.	• Adverse Device Effects (or other key events of interest, e.g., Heart Failure): In a timely manner but not later than 30 business days after becoming aware of the information • Adverse Events: In a timely manner but recommend within 30 business days after becoming aware of the information • Reporting required through the end of the study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• Upon request of sponsor

17.5. *Device Deficiencies*

Device deficiencies will be documented and reported to BSC. If possible, the device(s) under study should be returned to BSC for analysis following the commercial complaints process. Device deficiencies should also be documented in the patient's source records.

Device deficiencies should not be reported as AEs. Instead, they should be reported on the Device Deficiency eCRF. If an ADE/SADE results from a device deficiency, the ADE/SADE should be reported on the appropriate eCRF through study end.

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

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

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

18. Informed Consent

Subject participation in this clinical study is voluntary. Informed Consent is required from each subject. The investigator is responsible for ensuring that Informed Consent is obtained prior to the use of any non-standard of care, study specific assessment and/or testing. If all baseline and Index Procedure assessments/procedures are SOC, a subject may sign the ICF after receiving the WATCHMAN FLX Pro device.

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

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

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

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

Failure to obtain subject consent will be reported by BSC to the applicable regulatory authority according to their requirements (e.g., FDA requirement is within 5 working days of learning of such an event). Any violations of the informed consent process must be reported as deviations to the sponsor and local regulatory authorities (e.g., IRB), 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. The new version of the ICF must be approved by the IRB. Acceptance by Boston Scientific is required if changes to the revised ICF are requested by the site's IRB. The IRB will determine the subject population to be re-consented.

19. Committees

19.1. *Safety Monitoring Process*

The BSC personnel from the Medical Safety and Safety Trial Operation group review safety data as it is reported by the sites throughout the duration of the study. During scheduled monitoring activities, clinical research monitors further support this review through their review of source documents and other data information. The BSC Medical Safety and Safety teams include health care providers with expertise in cardiology and with the necessary therapeutic and subject matter expertise to evaluate and classify the events into the categories outlined above (Section **17**).

19.2. *Clinical Events Committee*

A Clinical Events Committee (CEC) will be used in this study. The CEC is an independent group of individuals with pertinent expertise, which reviews and adjudicates important endpoints and relevant adverse events reported by study investigators.

The CEC will review the following events for this study.

- Stroke (disabling and non-disabling; ischemic and hemorrhagic)
- Systemic Embolism
- Pericardial Effusion requiring pericardiocentesis or surgery
- All-cause mortality (cardiovascular and non-cardiovascular)
- Bleeding: ISTH major and non-major clinically significant bleeding including procedural (≤7 days post-procedure) and non-procedural (>7 days post-procedure)
- Other events, at the discretion of Boston Scientific

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

20. Suspension or Termination

20.1. *Premature Termination of the Study*

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

20.1.1. Criteria for Premature Termination of the Study

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

- Suspicion of an unacceptable risk, including serious health threat. In this case, the sponsor shall suspend the clinical investigation while the risk is assessed. The sponsor shall terminate the clinical investigation if an unacceptable risk which cannot be controlled is confirmed.
- Instructions by the IRB or regulatory authorities to suspend or terminate the clinical investigation.
- An enrollment rate far below expectation that prejudices the conclusion of the study.
- A decision on the part of Boston Scientific to suspend or discontinue development/marketing of the device.

20.2. *Termination of Study Participation by the Investigator or Withdrawal of IRB Approval*

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

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

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

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

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

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

Boston Scientific reserves the right to stop the inclusion of subjects at a study site at any time after the study initiation visit if no subjects have been enrolled for a period beyond 3 months after site initiation, or if the site has multiple or severe protocol violations/noncompliance without justification and/or fails to follow remedial actions.

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

21. Study Registration and Results

21.1. *Study Registration*

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

21.2. *Clinical Investigation Report*

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

21.3. *Publication Policy*

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

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

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

22. Reimbursement and Compensation for Subjects

22.1. *Compensation for Subject's Health Injury*

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

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24. Abbreviations and Definitions

24.1. *Abbreviations*

Abbreviations are shown in **Table 24-1**.

Table 24-1: Abbreviations

Abbreviation	Term
ADE	Adverse Device Effect
ACT	Activated Clotting Time
AE	Adverse Event
ADE	Adverse Device Event
AF	Atrial Fibrillation
ASADE	Anticipated serious adverse device effect
BSC	Boston Scientific Corporation
CE	Conformité Européenne
CEC	Clinical Event Committee
CHA_2DS_2-VASc	Congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/TIA, vascular disease, age 65–74 years, sex category
CI	Confidence Interval
CNS	Central Nervous System
CRF	Case Report Forms
CRO	Contract Research Organization
CT	Computerized Tomography
DAPT	Dual Antiplatelet Therapy
DOAC	Direct Oral Anticoagulant
DRT	Device Related Thrombus
EDC	Electronic Date Capture
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
GI	Gastrointestinal
HAS-BLED	Hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly, drugs/alcohol concomitantly
HCP	Health Care Personnel
ICE	Intracardiac Echocardiography
ICF	Informed Consent Form
IFU	Instructions for Use
IQRMP	Integrated Quality Risk Management Plan
IRB	Institutional Review Board
ISTH	International Society on Thrombosis and Haemostasis
ITT	Intent to Treat

Table 24-1: Abbreviations

Abbreviation	Term
LAA	Left Atrial Appendage
LAAC	Left Atrial Appendage Closure
LAAO	Left Atrial Appendage Occlusion
MRI	Magnetic Resonance Imaging
mRS	Modified Ranking Scale
NCT	National Clinical Trial
NSAID	Non-Steroidal Anti-Inflammatory Drugs
NVAF	Nonvalvular Atrial Fibrillation
OAC	Oral Anticoagulant
PET	Polyethylene Terephthalate
PFO	Patent Foramen Ovale
PG	Performance Goal
PDVF-HFP	polyvinylidene difluoride-hexafluoropropylene
RCT	Randomized controlled trial
RO	Radiopaque
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SE	Systemic Embolism
SEC	Spontaneous Echo Contrast
SOC	Standard of Care
TEE	Transesophageal Echocardiography
TIA	Transient Ischemic Attack
TSF	Technical Source Form
TTE	Transesophageal Doppler Echocardiography
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect
WM	WATCHMAN

24.2. *Definitions*

Terms are defined in **Table 24-2**. See **Table 24-1** for a list of abbreviations.

Table 24-2: Definitions

Term	Definition
ADVERSE DEVICE EFFECT (ADE)	Adverse event related to the use of an investigational medical device **Note 1**: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or 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.
Atrial Fibrillation (AF) Type	Paroxysmal: AF that terminates spontaneously or with intervention within 7 days of onset. Persistent: AF that is continuously sustained beyond 7 days, including episodes terminated by cardioversion (drugs or electrical cardioversion) after >_7 days. Permanent: AF that is accepted by the patient and physician, and no further attempts to restore/maintain sinus rhythm will be undertaken. Permanent AF represents a therapeutic attitude of the patient and physician rather than an inherent pathophysiological attribute of AF, and the term should not be used in the context of a rhythm control strategy with antiarrhythmic drug therapy or AF ablation. Should a rhythm control strategy be adopted, the arrhythmia would be re-classified as persistent AF.
BLEEDING [28-31]	**International Society on Thrombosis and Haemostasis (ISTH) Definitions** Clinically Relevant Non-Major Bleeding (AF and non-surgical VTE studies) Any sign or symptom of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for the ISTH definition of major bleeding but does meet at least one of the following criteria. • Requiring medical intervention by a healthcare professional • Leading to hospitalization or increased level of care • Prompting a face to face (i.e., not just a telephone or electronic communication) evaluation ISTH Major Bleeding in Non-Surgical Patients Defined as having a symptomatic presentation and one or more of the following. • Fatal bleeding, AND/OR • Bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome, AND/OR • Bleeding causing a fall in hemoglobin level of 20 g L^{-1} (1.24 mmol L^{-1}) or more, or leading to transfusion of two or more units of whole blood or red cells **Bleeding Academic Research Consortium (BARC) Definitions** 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.

<table>
<tr><td></td><td>
• Requiring nonsurgical, medical intervention by a health-care professional, AND/OR
• Leading to hospitalization or increased level of care, AND/OR
• Prompting evaluation
<u>Type 3</u>
• 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 not include intraspinal)
  • Subcategories confirmed by autopsy or imaging or lumbar puncture
  • Intraocular bleed compromising vision
<u>Type 4</u>
• Coronary bypass graft-related bleeding
• Perioperative intracranial bleeding within 48h
• 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
<u>Type 5</u>
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
</td></tr>
<tr><td>CARDIAC TAMPONADE</td><td>Evidence of a new pericardial effusion associated with hemodynamic instability and clearly related to the index procedure. Clinical syndrome caused by the accumulation of fluid in the pericardial space, resulting in reduced ventricular filling and subsequent hemodynamic compromise.</td></tr>
<tr><td>CHA2DS2-VASc score</td><td>
<table>
<tr><th colspan="2">CHA_2DS_2-VASc score Risk Factors and Definitions[a]</th><th>Points Awarded</th><th>Further definition</th></tr>
<tr><td>C</td><td>Congestive Heart Failure</td><td>1</td><td>Clinical heart failure (HF), or objective evidence of moderate to severe left ventricular (LV) dysfunction[b], or hypertrophic cardiomyopathy (HCM)</td></tr>
<tr><td>H</td><td>Hypertension</td><td>1</td><td>Hypertension or on antihypertensive therapy</td></tr>
<tr><td>A</td><td>Age 75 years or older</td><td>2</td><td></td></tr>
<tr><td>D</td><td>Diabetes Mellitus</td><td>1</td><td>Treatment with oral hypoglycemic drugs and/or insulin or fasting blood glucose >125 mg/dl (7 mmol/L)</td></tr>
<tr><td>S</td><td>Stroke</td><td>2</td><td>Previous stroke, TIA, or thromboembolism</td></tr>
<tr><td>V</td><td>Vascular Disease</td><td>1</td><td>Angiographically significant coronary artery disease (CAD), previous myocardial infarction (MI), peripheral artery disease (PAD), or aortic plaque</td></tr>
<tr><td>A</td><td>Age 65-74 years</td><td>1</td><td></td></tr>
<tr><td>Sc</td><td>Sex Category (female)</td><td>1</td><td></td></tr>
<tr><td colspan="2">Maximum Score</td><td>9</td><td></td></tr>
</table>
</td></tr>
</table>

	[a]For further detail, please reference Table 8 from the 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS); European Heart Journal (2020) 42, 373-498 doi:10.1093/eurheartj/ehaa612 [b]LV dysfunction: Severe <35%; Moderate 35-40%; Mild: 41-49%; Normal >50%.
Correct Anatomical Position	Refers to the deployment of the WATCHMAN FLX Pro implant within the Left Atrial Appendage. It does not imply or require proper positioning within the LAA nor does it exclude implant embolization after final implant release.
DEATH	**Cardiovascular Death** Any one of the following criteria is met. • Death due to proximate cardiac cause (e.g., myocardial infarction, cardiac tamponade, worsening heart failure, endocarditis, etc.) • Death caused by noncoronary, non-CNS vascular conditions such as pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular disease • Death from vascular CNS causes o Hemorrhagic stroke o Ischemic stroke • All-cause mortality during the index procedure, any procedure-related death within 30 days after the index procedure or during postoperative hospitalization for the index procedure (if >30 days), including those related to a complication of the procedure or treatment for a complication of the procedure • Unexplained death (see below) **Non-cardiovascular Death** • Any death in which the primary cause of death is clearly related to another condition (e.g., trauma, cancer, suicide) **Unexplained Death** • Sudden or unwitnessed death defined as a non-traumatic, unexpected fatal event occurring within one hour of the onset of symptoms in an apparently healthy subject. If death is not witnessed, the definition applies when the victim was in good health 24 hours before the event. • Death of unknown causes
DEVICE DEFICIENCY	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. **Note 1**: Device deficiencies include malfunctions, use errors, and inadequate labeling.
DEVICE EMBOLIZATION	Defined as movement of the device during or after deployment such that it dislodges and entirely leaves the LAA or completely loses contact with the LAA.
DEVICE MIGRATION	Defined as shifting of the implant within the LAA to create an inadequate seal where the gap is greater than 5mm at 45 days or later and the physician must intervene (e.g., adjust patient's anticoagulant regimen).
DEVICE RELATED THROMBUS	Thrombus formation on the atrial facing side of the device, possibly resulting in the need for anticoagulation and/or hospitalization.
DEVICE SUCCESS	Defined as implantation of a WATCHMAN FLX device in the correct anatomical position and without in-hospital mortality
ENROLLMENT GUIDE	A guidance document provided to sites in order to communicate which trial subsets are eligible for enrollment or subsets that are no longer eligible for enrollment.
EMBOLISM	Examples include a free-flowing blood clot or lesion material that is located in the systemic or pulmonary circulation. Embolism may be manifested by a neurological event or a noncerebral embolic event.

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 causes 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.
NON-VALVULAR ATRIAL FIBRILLATION	Atrial fibrillation in the absence of moderate-to-severe mitral stenosis or in the absence of a mechanical heart valve.
PRIMARY ANALYSIS SUBSET	The Primary Analysis Subset consists of data from the initial 500 enrolled subjects.
PROCEDURE-RELATED EVENTS	Events occurring during or as a direct result of the index procedure.
SERIOUS ADVERSE EVENT (SAE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Adverse event that: • Led to death, • Led to serious deterioration in the health of the subject as defined by either: o 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.
SERIOUS ADVERSE DEVICE EFFECT (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event
SOURCE DATA (per ISO 14155:2011)	All information in original records of clinical findings, observations, or other activities in a clinical investigation, necessary for the reconstruction and evaluation of the clinical investigation
SOURCE DOCUMENT (per ISO 14155:2011)	Printed, optical or electronic document containing source data. Examples: Hospital records, laboratory notes, device accountability records, photograhic negatives, radiographs, records kept at the investigation center, at the laboratories and at the medico-technical departments involvced in the clinical investigation.
STROKE[32,33]	**Stroke Definition** Stroke is defined by one of following. • Duration of a focal or global neurological deficit ≥24 h • Duration of a focal or global neurological deficit <24 h, if available neuroimaging documents a new hemorrhage or infarct • A neurological deficit resulting in death **Stroke Classification** Ischemic Stroke o An episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction.

	Hemorrhagic Stroke o *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. o *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. Not Otherwise Specified o 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. **Stroke Diagnostic Criteria** • Rapid onset of a focal or global neurological deficit with at least one of the following: change in level of consciousness, hemiplegia, hemiparesis, numbness or sensory loss affecting one side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke • Duration of a focal or global neurological deficit ≥24 h; OR <24 h, if therapeutic intervention(s) were performed (e.g., thrombolytic therapy or intracranial angioplasty); OR available neuroimaging documents a new hemorrhage or infarct; OR the neurological deficit results in death • No other readily identifiable non-stroke cause for the clinical presentation (e.g., brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences) • Confirmation of the diagnosis by at least one of the following. o Neurology or neurosurgical specialist o Neuroimaging procedure (MRI or CT scan or cerebral angiography) o Lumbar puncture (i.e., spinal fluid analysis diagnostic of intracranial hemorrhage) **Stroke Definitions** Diagnosis as above, preferably with positive neuroimaging study • Non-disabling: Modified Rankin Scale (mRS) score <2 at 90 days OR one that does not result in an increase of at least one mRS category from an individual's pre-stroke baseline • Disabling: Modified Rankin Scale score ≥2 at 90 days AND an increase of at least one mRS category from an individual's pre-stroke baseline **Note 1:** Modified Rankin Scale assessments should be made by qualified individuals according to a certification process. **Note 2:** Assessment of the mRS score should occur at baseline; mRS also should be performed after a stroke and at 90 days after the onset of any stroke.
SYSTEMIC EMBOLISM	Acute systemic arterial insufficiency or occlusion of the extremities or any non-CNS organ associated with clinical, imaging, surgical/autopsy evidence of arterial occlusion in the absence of other likely mechanism (e.g., trauma, atherosclerosis, or instrumentation). When there is presence of prior peripheral artery disease, angiographic or surgical or autopsy evidence is required to show abrupt arterial occlusion.
TRANSIENT ISCHEMIC ATTACK (TIA)	Any neurological deficit not satisfying the criteria for stroke (see above for definition of stroke), specifically: • Duration of a deficit is <24 h; AND • Neuroimaging does not document a new hemorrhage or infarct **Note 1:** The difference between TIA and ischemic stroke is the presence of tissue damage or new sensory-motor deficit persisting >24 hours. By definition, TIA does not produce lasting disability.
UNANTICIPATED SERIOUS ADVERSE DEVICE EFFECT (USADE)	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:** An anticipated serious adverse device effect is an effect which by its nature, incidence, severity, or outcome has been identified in the risk analysis report.

VALVULAR ATRIAL FIBRILLATION	Atrial fibrillation in the setting of moderate-to-severe mitral stenosis (potentially requiring surgical intervention) or in the presence of an artificial (mechanical) heart valve.
VULNERABLE SUBJECT (per ISO 14155:2020)	Vulnerable subjects are individuals who are unable to fully understand all aspects of the investigation that are relevant to the decision to participate, or who could be manipulated or unduly influenced as a result of a compromised position, expectation of benefits or fear of retaliatory response.