A Pilot Study to Assess WATCHMAN FLX™ Pro Implants by Cardiac Computed Tomography, Magnetic Resonance Imaging and Transesophageal Echocardiography: WATCHMAN FLX Pro CT

WATCHMAN FLX Pro CT
S2517
CLINICAL INVESTIGATION PLAN

National Clinical Trial (NCT) Identifier Number: NCT05567172

Sponsor:	Boston Scientific Corporation 300 Boston Scientific Way Marlborough, MA 01752 USA International Representative Boston Scientific International SA 2 Rue René Caudron, Bâtiment H 78960 Voisins-le-Bretonneux, France

Contact Information

Role	Contact
Clinical Contacts	Nilou Zilinek, MS Clinical Trial Manager - WATCHMAN Boston Scientific Corporation 100 Boston Scientific Way, M60 Marlborough, MA 01752 Kellie Windle Director, Clinical Trials - WATCHMAN Boston Scientific Corporation 100 Boston Scientific Way, M60 Marlborough, MA 01752
Study Coordinating Principal Investigator	Prof Jens Erik Nielsen-Kudsk, MD Department of Cardiology Aarhus University Hospital Palle Juul-Jensens Boulevard 99, DK-8200 Aarhus N Aarhus, Denmark
Vendors/Labs/ External Organizations	A list of vendors/laboratories/external organizations involved in the trial is maintained by the sponsor.

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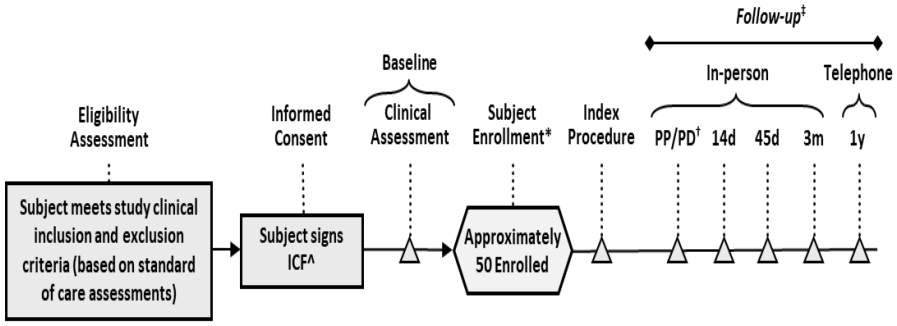
Revision Version	Protocol Date	Template number and version	Protocol Section Modified	Summary of Changes	Justification for Modification
A	02-Nov-2022	Template 90702637_Rev/Ver AQ	N/A	N/A	Initial Release
B	06-Feb-23	Template 90702637_Rev/Ver AQ	Cover page	• Updated the study number to S2517	Internal BSC administrative update
			6.1	• Updated table 6.1-1 to note primary endpoint header more clearly	Clarification

Revision Version	Protocol Date	Template number and version	Protocol Section Modified	Summary of Changes	Justification for Modification
			8.2	• Combined IC2 and IC3 in table 8.2-1 to state the device indication more clearly	Clarification
			10.1	• Added pregnancy testing into table 10.1-1 after signing of ICF and prior to enrollment	Danish Competent Authority request
			10.1	• Increased time period for baseline imaging assessment from 7 to 14 days	Time increased to help site for scheduling of subjects
			10.1	• Changed the time baseline serum creatinine should be drawn from 180 to 30 days prior to consent	To help the site consolidate all baseline labs
			10.2	• Added language about required pregnancy testing post signing of IC and prior to enrollment as well as details on use of contraceptives during the study	Danish Competent Authority request
			10.4 10.8.1 10.8.2	• Added volume of blood drawn for labs as well as list of analyses done for each f/u visit	Danish Competent Authority request
			18.6	• Added ISO 14155:2020, Medical Device Regulation (EU) 2017/745, and MDCG 2020-10/1 reporting requirements	Danish Competent Authority request
			Throughout	• Added language to clarify that Subjects who are enrolled but not implanted with a WATCHMAN FLX Pro device will be followed for safety through 12 months after the initial attempted implant procedure by telephone or review of clinical files	Clarification
C	**12-Apr-23**	Template 90702637_Rev/Ver AQ	18.6	• Section updated to remove reference to 64 MPDG and to add language regarding annual safety report	Clarification and correction

Revision Version	Protocol Date	Template number and version	Protocol Section Modified	Summary of Changes	Justification for Modification
			8.3	• Removed reference to MRI in Exclusion Criteria #3 to be consistent with EC #3 in the synopsis	Correction
D	**08-Nov-23**	Template 90702637_Rev/Ver AS	Throughout	• Change number of subjects from 25 to 50	Study expansion
			Throughout	• Updated language in applicable sections to keep in line with protocol template	Protocol template revision

2. Protocol Synopsis

A Pilot Study to Assess WATCHMAN FLX™ Pro Implants by Cardiac Computed Tomography, Magnetic Resonance Imaging and Transesophageal Echocardiography: WATCHMAN FLX™ Pro CT	
Study Objective(s)	The primary objective of this study is to measure device tissue coverage post-implantation of the WATCHMAN FLX™ Pro Left Atrial Appendage Closure (LAAC) Device (WATCHMAN FLX Pro) using the serial advanced imaging modalities of cardiac computed tomography (CT) and transesophageal echocardiography (TEE) and assess its relationship, if any, to clinical events.
Planned Indication(s) for Use	As per the clinical Instructions for Use (IFU), WATCHMAN FLX Pro is intended to prevent thrombus embolization from the left atrial appendage and reduce the risk of life-threatening bleeding events in patients with non-valvular atrial fibrillation who are eligible for anticoagulation therapy or who have a contraindication to anticoagulation therapy.
Device Under Study (Test Device)	Device under study (test device) include the 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 any commercially available WATCHMAN® Access System (access sheath and dilator).
Study Design	WATCHMAN FLX™ Pro CT is a prospective, single-arm, single-center, premarket investigation to assess device tissue coverage in subjects with non-valvular atrial fibrillation (AF) who receive the WATCHMAN FLX Pro device to reduce the risk of stroke. Serial advanced imaging modalities such as CT and TEE will be used. A core laboratory will independently assess select results. A subject is considered enrolled in the study when the subject or the subject's legally authorized representative signs an Informed Consent Form (ICF) approved by the Independent Ethics Committee (IEC). Up to 50 subjects in whom placement of a WATCHMAN FLX Pro device is attempted will be enrolled. A baseline assessment including TEE and/or CT imaging with optional cardiac magnetic resonance imaging (MRI) will be done

A Pilot Study to Assess WATCHMAN FLX™ Pro Implants by Cardiac Computed Tomography, Magnetic Resonance Imaging and Transesophageal Echocardiography: WATCHMAN FLX™ Pro CT	
	within 14 days prior to the implant procedure following core laboratory guidelines. Follow-up clinical assessment and imaging will occur at 14 days, 45 days, and 3 months post implant procedure; only clinical assessment will be required at 12 months (unless an in-person assessment is required based on other data). Subjects who are enrolled but not implanted with a WATCHMAN FLX Pro LAAC device will be followed for safety through 12 months after the initial attempted implant procedure by telephone or review of clinical files but will not undergo imaging assessments or evaluation of biochemical markers including measures of coagulation, platelet and endothelial activation and inflammation. The study design is summarized below.  ^ Subjects must sign the study ICF before any study-specific assessments can be carried out. * Subjects who provide informed consent are considered enrolled. Subjects of childbearing potential must have a negative pregnancy test after signing ICF and before the implant procedure. † Post-procedure/Pre-discharge ‡ Visits are in-person through 3 months and in-person (preferred) or via telephone interview at 1 year. **WATCHMAN FLX Pro CT Study Design Overview** Eligibility is determined per standard of care. Any additional study specific testing to verify inclusion/exclusion criteria must be done after the ICF is signed. Abbreviation: ICF=Informed Consent Form
Planned Number of Subjects	Up to 50 subjects in whom placement of a WATCHMAN FLX Pro device is attempted will be enrolled.

A Pilot Study to Assess WATCHMAN FLX™ Pro Implants by Cardiac Computed Tomography, Magnetic Resonance Imaging and Transesophageal Echocardiography: WATCHMAN FLX™ Pro CT	
Planned Number of Centers / Countries	There will be 1 investigational center in western Europe.
Primary Endpoint	Device surface morphology (inclusive of tissue coverage) post implant procedure as assessed over time using the serial advanced imaging modalities of cardiac computed tomography (CT) and transesophageal echocardiography (TEE) with data evaluated by an independent core laboratory.
Additional Measurements	Additional measurements will be collected peri- and post-procedure, predischarge, and at 14 days, 45 days, 3 months, and 12 months (if needed) after the implant procedure, unless otherwise specified below. • Safety endpoints (adjudicated by an independent Clinical Events Committee [CEC]): o All-cause mortality (cardiovascular/unknown and non-cardiovascular) o Stroke (disabling and non-disabling; ischemic and hemorrhagic; see **Note 2**) o Systemic embolism o Bleeding: International Society on Thrombosis and Haemostasis (ISTH) major and non-major clinically significant[a] ▪ Procedural bleeding (≤7 days post-procedure) ▪ Non-procedural bleeding (>7 days post-procedure) o Pericardial effusion/tamponade requiring pericardiocentesis or surgery **Note 2:** For subjects diagnosed with a neurological event (e.g., stroke, transient ischemic attack [TIA]), Modified Rankin Scale (mRS) and National Institutes of Health Stroke Scale (NIHSS) should be performed after the event. It is recommended that the subject be contacted regarding mRS assessment at 90±14 days following any suspected stroke; the simplified mRS questionnaire[b] may be used for this follow-up assessment. It is also recommended that imaging be performed after the event to screen for device

A Pilot Study to Assess WATCHMAN FLX™ Pro Implants by Cardiac Computed Tomography, Magnetic Resonance Imaging and Transesophageal Echocardiography: WATCHMAN FLX™ Pro CT	
	related thrombus. If performed, imaging results should be sent to the core laboratory. • Device Success: defined as implantation of a WATCHMAN FLX Pro device without in-hospital mortality • Assessments by serial imaging modalities (CT and TEE; cardiac MRI optional) at 14 days, 45 days, and 3 months; data will be evaluated by an independent core lab o Device seal post implant procedure (see **Note 3** and **Note 4**) o Device-related thrombus (including hypoattenuated thickening [HAT] per CT analysis) **Note 3:** Results are classified as no leak, leak >0 and ≤5mm, or leak >5mm. **Note 4:** TEE is required at 12 months if the 3-month TEE assessment suggests a leak > 5mm or the 3-month CT assessment suggests a leak > 3mm; results must be sent to the core laboratory. • 4D cardiac MRI flow analysis (if available) of the left atrium (LA) and LAA before and serially after device implant at 14 days, 45 days, and 3 months; data will be evaluated by an independent core lab • Changes compared to baseline in measures of biochemical markers including coagulation, platelet and endothelial activation and inflammation at 14 days, 45 days, and 3 months post implant procedure; correlations with morphological findings from imaging assessment of the device surface will be examined a: Schulman S and Kearon C. *J Thromb Haemost* 2005;3:692-694 Kaatz S, et al. *J Thromb Haemost* 2015;13:2119-26 b: Bruno A, et al. *Stroke* 2011;42:2276-2279
Follow-up Schedule	Follow-up for all subjects will occur post-implant on the procedure day, at predischarge, and at 14 days, 45 days, 3 months, and 12 months post implant procedure. Follow-up will include clinical assessments at all time points and imaging assessments at 14 days, 45 days, and 3 months. Subjects who are enrolled but not implanted with a WATCHMAN FLX Pro device in the correct position will be followed for safety through 12 months after the initial attempted implant procedure by telephone or review of clinical files but will

A Pilot Study to Assess WATCHMAN FLX™ Pro Implants by Cardiac Computed Tomography, Magnetic Resonance Imaging and Transesophageal Echocardiography: WATCHMAN FLX™ Pro CT	
	not undergo imaging assessments or evaluation of biochemical markers including measures of coagulation, platelet and endothelial activation and inflammation. The study will be considered complete after all available subjects have finished the 12-month follow-up visit.
Study Duration	Subjects will be followed for 12 months after the implant procedure. Due to the addition of 25 more patients to the initial 25 patients implanted, the enrollment period will be extended to minimally 15 months; therefore, the total study duration from first subject enrolled to last subject follow-up is estimated to be at least 28 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 per the laws of their respective geography. 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) and who has a relative or absolute contraindication to anticoagulation. IC3. Subject is deemed suitable for the protocol-defined pharmacologic regimen. 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.
Exclusion Criteria	Exclusion criteria are listed below. EC1. 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. EC2. Subject has eGFR <30 mL/min (chronic kidney disease stage IV or stage V). EC3. Subject is contraindicated for TEE.

A Pilot Study to Assess WATCHMAN FLX™ Pro Implants by Cardiac Computed Tomography, Magnetic Resonance Imaging and Transesophageal Echocardiography: WATCHMAN FLX™ Pro CT	
	EC4. Subject requires long-term anticoagulation therapy for reasons other than AF-related stroke risk reduction (e.g., due to an underlying hypercoagulable state). EC5. Subject had or is planning to have any cardiac or non-cardiac intervention or surgical procedure within 30 days prior to or 60 days after implant (including, but not limited to, cardioversion, percutaneous coronary intervention, cardiac ablation, cataract surgery, etc.). EC6. Subject had a prior stroke (of any cause, whether ischemic or hemorrhagic) or TIA within the 30 days prior to enrollment. EC7. Subject had a prior major bleeding event per ISTH definitions within the 30 days prior to enrollment. Lack of resolution of related clinical sequelae or planned and pending interventions to resolve bleeding/bleeding source are a further exclusion regardless of timing of the bleeding event. EC8. Subject has an active bleed. EC9. Subject has a reversible cause for AF or has transient AF. EC10. Subject has no LAA or the LAA is surgically ligated. EC11. Subject has had a myocardial infarction (MI) documented in the clinical record as either a non-ST elevation MI (NSTEMI) or as an ST-elevation MI (STEMI), with or without intervention, within 30 days prior to enrollment. EC12. Subject has a history of atrial septal repair or has an atrial septal defect/patent foramen ovale (ASD/PFO) device. EC13. Subject has a known contraindication to percutaneous catheterization procedure. EC14. Subject has a cardiac tumor. EC15. Subject has signs/symptoms of acute or chronic pericarditis. EC16. Subject has an active infection. EC17. There is evidence of tamponade physiology. EC18. Subject has New York Heart Association Class IV congestive heart failure at the time of enrollment. EC19. 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).

A Pilot Study to Assess WATCHMAN FLX™ Pro Implants by Cardiac Computed Tomography, Magnetic Resonance Imaging and Transesophageal Echocardiography: WATCHMAN FLX™ Pro CT	
	EC20. Subject has a documented life expectancy of less than 6 months.
Adjunctive Pharmacologic Therapy	Subjects must be treated with single antiplatelet therapy (SAPT; aspirin or $P2Y_{12}$ inhibitor) for at least 3 months following WATCHMAN FLX Pro implantation.
Multiple Interventions During Implant Procedure	No concomitant procedures are to be performed at the time of the WATCHMAN FLX Pro implant procedure with the exception of implantable loop recorder implants/explants. This includes, but is not limited to, cardiac ablation procedures, transcutaneous valve procedures, cardioversions, coronary stent implantation, pacemaker or implantable cardioverter defibrillator generator change, etc.
Statistical Methods	
Analysis Sets	Analysis sets are listed below. - Intention-To-Treat (ITT): This population includes all subjects who sign an ICF and are enrolled in the study, regardless of whether the study device is implanted. - Implanted: This population includes all subjects who sign an ICF, are enrolled in the study, and are successfully implanted with the study device in the correct position.
Statistical Hypothesis	There is no formal statistical hypothesis for this observational, single-arm study. No statistical inference will be made in the study.
Methods	Outcomes in the overall treatment cohort 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).

3. Table of Contents

3.1. *Table of Figures*

3.2. *Table of Tables*

4. Introduction

This protocol specifies procedures for and contains information relevant to the clinical study entitled "A Pilot Study to Assess WATCHMAN FLX™ Pro Implants by Cardiac Computed Tomography, Magnetic Resonance Imaging and Transesophageal Echocardiography" (WATCHMAN FLX™ Pro CT). The study will measure device tissue coverage post insertion of the WATCHMAN FLX™ Pro Left Atrial Appendage Closure Device implant (WATCHMAN FLX Pro implant) and assess its relationship, if any, to clinical events. Serial advanced imaging modalities to be used in the study include cardiac computed tomography (CT) and transesophageal echocardiography (TEE). Up to 50 consented subjects will be enrolled. Data for subjects receiving the WATCHMAN FLX Pro implant will be collected over 12 months.

Background information is provided below in Section **4.1**. Additional information on the device under study (test device) can be found in Section **5**. Additional information on study design can be found in Section **7**.

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 (WATCHMAN FLX) 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 2015 and FDA approval in 2020[27].

4.1.3. New Features of WATCHMAN FLX Pro

Key differences between WATCHMAN FLX Pro and predecessor WATCHMAN products include the addition of a 40mm size implant to accommodate larger sizes of LAA, as well as a PVDF-HFP coating on the implant surface, designed to promote endothelialization and thereby reduce thrombus formation.

Double device closure for large and bilobar LAA has been reported with WATCHMAN and WATCHMAN FLX.[28-33] While implant success was 100%, peri-device leak was reported in 2 of the 8 patients in a case series by Alkhouli et al. (2020),[28] while another case series in 7 patients by Chen et al. (2022)[29] documented the persistence of of peri-device leak in two of the patients through 2 years. While not a common practice, these studies highlight that the WATCHMAN and WATCHMAN FLX implant sizes do not cover the needs of the full range of patient anatomies. The need for larger LAAO devices was also noted by So et al. (2020)[34]

in a publication of outcomes related to implantation of LAmbre covers in 27 patients with LAA >31mm in three centers. Citing the limitation of being able to implant WATCHMAN in LAA >31mm, the physicians solely relied on the LAmbre device's anchoring mechanism to implant in LAAs of up to 40mm rather than oversizing as recommended for that device. The practice led to peri-device leak in 33% of cases. These experiences highlight the need for a LAAO device properly sized to the anatomy. No size-specific adverse events were identified for the occlusion of large LAA.

Device Thrombosis or Device-Related Thrombus (DRT) is one of the complications associated with percutaneous LAAO. This term describes any thrombosis that originates from the device itself. DRT can arise on the surface of any foreign body.[35] Prevention of device related thrombus is critical in the initial phase after successful device implantation. Device related thrombus risk is highest until the device is covered with endothelial cells.[36] The potential risk to patient health is that the DRT will embolize, leading to ischemic stroke or systemic embolism. To protect against device thrombosis, various regimens of antithrombotic regimens have been used.[36] DRT can be detected through imaging (e.g., trans-esophageal echocardiogram or TEE).[37] The incidence of DRT is up to 3.8% for LAA devices (351/10,153 [3.8%, 95% CI 3.1% to 4.6%, $I^2 = 56.8$]), according to a meta-analysis of 66 LAAO studies.[38] The majority of DRT events (85%) were detected after 45 days. Device-related thrombosis puts patients at risk for ischemic events. As calculated by the same meta-analysis, in studies that compared outcomes of patients with and without DRT (32 studies; n = 7,689), the pooled incidence of ischemic events was 13.2% (37 of 280) in patients with DRT and 3.8% (285 of 7,399) in those without DRT (OR: 5.27, 95% CI: 3.66 to 7.59; $p < 0.001$, $I^2 = 0$).

The same fabric used in the WATCHMAN family of LAAO devices, polyethylene terephthalate (PET), has a decades-long history of use for vascular grafts and has been coated with various agents in efforts to improve graft patency. A literature search was performed to identify potential risks associated with coating PET in cardiovascular implants with PVDF-HFP or related fluoropolymer compounds. Two studies comparing fluoropolymer-coated PET vascular grafts to expanded polytetrafluoroethylene (ePTFE) vascular grafts for peripheral vasculature bypass were identified.[39,40] The specific fluoropolymer was not noted, and the surface was sealed with gelatin, which would be expected to further impact thrombogenicity. In a multicenter RCT comparing use of ePTFE grafts (n=107) to fluoropolymer-coated PET grafts (n=91) for use in femorofemoral crossover bypass surgery, no coating-specific risks were identified and primary patency rate of the two grafts was similar (log rank test: p=0.35) by 24 months.[39] In the second multicenter RCT of femoropopliteal bypass in 129 patients, graft thrombosis developed in the first month in 22 of 61 (36%) patients receiving fluoropolymer-coated grafts compared to six of 68 (8.8%) patients receiving PTFE, accounting for a difference in primary patency at 24 months (p=0.002).[40] Risk factors for reduced patency were critical limb ischemia, below-knee anastomoses, and smaller (6mm diameter) grafts. It should be noted that small diameter and low blood flow are generally risk factors for thrombus formation, and these conditions are not analogous to the conditions experienced by LAAO devices. Furthermore, these grafts have limited opportunity for endothelialization due to contact of the graft with vascular tissue

only at the anastomosis sites, also a creating dynamic quite different than that found in LAAO devices, which have circumferential contact with the LAA. Therefore, the key takeaway from these studies is that no embolic or biocompatibility risks related to the coating were identified through these studies.

4.1.4. Cardiac Imaging

Healing post LAAO includes endothelialization of the LAAO device. In a preclinical canine model, the PET fabric membranes of implanted WATCHMAN devices showed an organized neoendocardial surface at 45 days with endothelialization well under way by 90 days[28]. Human necropsy hearts showed similar healing stages, though animal healing was faster[28].

In patients, pre-procedural anatomical assessment of the LAA with TEE, CT, or cardiac magnetic resonance imaging (MRI) is used to determine the technical feasibility and safety of LAA occlusion, including device sizing and optimal implant positioning. A multimodality integrated approach including angiography, TEE, and/or intracardiac echocardiography (ICE) provides intraprocedural guidance and confirmation of LAA closure[29-31]. After the procedure, imaging surveillance at follow-up allows assessment of device tissue coverage, peri-device leaks, and device-related thrombus (DRT), which has been observed with various LAAO devices and may be associated with late thromboembolic events[32-37].

The WATCHMAN FLX Instructions for Use (IFU) recommends use of TEE at 45 days post device implant to check for the presence of intra-cardiac thrombus as well as to detect and measure any residual flow around the device. The ongoing WATCHMAN FLX CT study (NCT05324371) is evaluating device tissue coverage at several time points in addition to the recommended 45 days using serial CT and TEE and assessing its relationship, if any, to clinical events.

The device under study (test device) WATCHMAN FLX Pro device is an iteration of WATCHMAN FLX. The implant includes updated components, and the revised delivery system offers 5[OBJ]). The WATCHMAN FLX Pro CT study (NCT05567172) will use CT and TEE to measure device tissue coverage after placement of the WATCHMAN FLX Pro implant and will assess the relationship, if any, of device tissue coverage to clinical events.

4.2. *Study Rationale*

The iterative WATCHMAN FLX Pro device investigated in this study potentially provides several performance and safety features beyond that of earlier WATCHMAN versions (see Section **5**). Anticipated risks and benefits known to be associated with the WATCHMAN family of devices and with participation in this clinical investigation when this protocol was written are summarized in the Investigator Brochure (IB) and in Section **17** of this document. The risk-benefit analysis concluded that the known risks associated with the procedure, and specifically the use of the WATCHMAN device, have been mitigated to acceptable limits. The available Sponsor-provided training program (Section **15.4.2**) further mitigates risk.

It is therefore determined that:

- All applicable risks have been addressed through appropriate testing and any residual risks are acceptable when weighed against the potential benefits to the subject.
- The potential benefits of the use of the device out-weigh the risks.

Note: The term "WATCHMAN" is used generically and includes various device iterations.

5. Device Description

5.1. *Device Under Study (Test Device)*

The device under study (test device) WATCHMAN FLX™ Pro device (manufactured by Boston Scientific Corporation, Marlborough, MA, USA) has two main parts: a WATCHMAN FLX™ Pro Left Atrial Appendage Closure (LAAC) Device implant and a WATCHMAN FLX Pro Delivery System for implant introduction and placement. They are summarized in **Table 5.1-1** below.

Table 5.1-1: Device Under Study (Test Device)

Device Name/Size	Description
WATCHMAN FLX™ Pro Left Atrial Appendage Closure Device implant. Sizes: 20mm, 24mm, 27mm, 31mm, 35mm, and 40mm	Closure device components: • Self-expanding nitinol frame structure with fixation anchors around the perimeter. • A permeable polyester fabric (polyethylene terephthalate) that covers the atrial-facing implant surface. WATCHMAN FLX™ Pro Left Atrial Appendage Closure Device implant is preloaded in the WATCHMAN FLX™ Pro Delivery System. This is introduced via femoral venous access and placed in the left atrial appendage after crossing the inter-atrial septum. WATCHMAN FLX™ Pro Delivery System • Allows delivery and positioning of the transcatheter closure device.

Per the investigational product Instructions for Use (IFU), the WATCHMAN FLX™ Pro device is intended to prevent thrombus embolization from the left atrial appendage (LAA) and reduce the risk of life-threatening bleeding events in patients with non-valvular atrial fibrillation who are eligible for anticoagulation therapy or who have a contraindication to anticoagulation therapy. Please see the investigational product IFU for any contraindications.

5.2. *Test Device – WATCHMAN FLX Pro LAAC Device Implant and Delivery System*

The WATCHMAN FLX Pro LAAC Device implant (Panel A in **Figure 5.2-1**) 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. The fabric is dip coated in a fluoropolymer, specifically polyvinylidene difluoride-hexafluoropropylene (PVDF-HFP), which due to its thromboresistance and low inflammatory response, may promote faster endothelization and healing. Three proximal radiopaque markers are aligned at the plane of maximum diameter of the implant to aid in fluoroscopic assessment of the WATCHMAN FLX Pro Device. **Table 5.2-1** shows the six available implant sizes. Appropriate sizing is determined by LAA measurements using fluoroscopy and echocardiographic guidance.

The delivery system (Panel B in **Figure 5.2-1**) 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.

Table 5.2-1: WATCHMAN FLX Pro Device Selection

Maximum Left Atrial Appendage Ostium Width (mm) and/or Deployed Closure Device Diameter (mm)	Closure Device Diameter (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

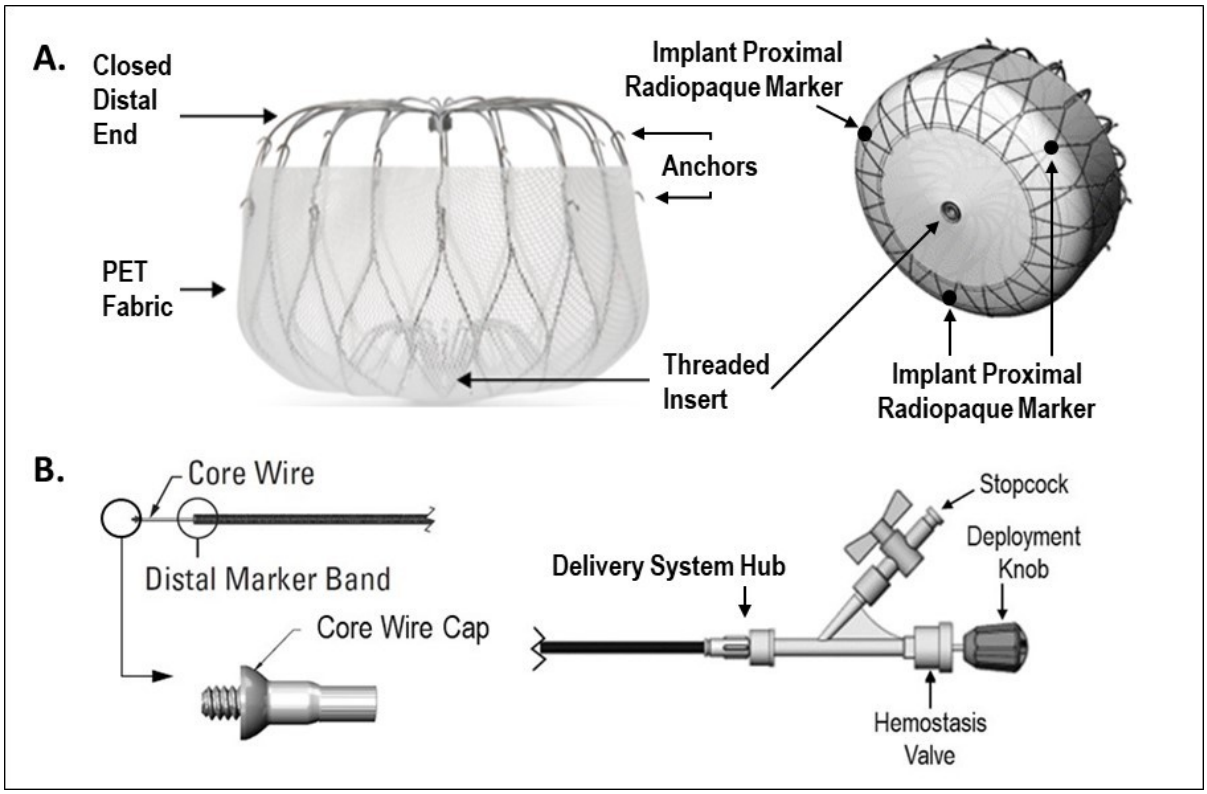


Figure 5.2-1: WATCHMAN FLX Pro Device

A: LAA Closure Device Implant; B: Delivery System
Abbreviations: LAA=left atrial appendage; PET=polyethylene terephthalate
Source: WATCHMAN FLX Pro Instructions for Use

The WATCHMAN FLX Pro LAA Closure Device implant is pre-loaded on the delivery system and is constrained within the catheter until deployment in the LAA. This preloaded system will be labeled for investigational use. Devices will be identified by Universal Product Number (UPN) and batch number. In the WATCHMAN FLX Pro CT study, this preloaded delivery system may be used in conjunction with any version of the commercially available WATCHMAN® Access System or WATCHMAN TruSeal Access System (access sheath and dilator; Section **5.3**) to facilitate device placement in the LAA via femoral venous access and crossing of the inter-atrial septum into the left atrium. The implant is deployed by loosening the hemostasis valve on the delivery catheter and retracting the delivery 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 clinical IFU.

The WATCHMAN FLX device offered additional features compared to the predicate WATCHMAN™ Left Atrial Appendage Closure Device with Delivery System. The

WATCHMAN FLX Pro device offers added features compared to the WATCHMAN FLX device. The additional features are summarized in **Table 5.2-2**.

Table 5.2-2: WATCHMAN – Additional Features

Feature	Purpose
WATCHMAN to WATCHMAN FLX[a]	
Closed distal end	Provides improved deployment stability and control, with atraumatic distal structure
Fully recapturable and re-deployable	Decrease the number of devices used and sheath exchanges per case, which may reduce procedure time and complications associated with sheath exchange
Decreased recapture force	Improve user experience
Increased conformability	Create a better LAA seal due to the increased number of contact points around the LAA ostium, which was designed to promote short-term healing
Decreased exposed metal volume on proximal face	May promote short-term healing
Enhanced radiopacity	Improve visibility under fluoroscopy
Smaller and larger device sizes	Allow for treatment of complex, shallow LAA anatomies
Greater overlap in device sizing choices	Allow for treatment of a wider range of appendage sizes
WATCHMAN FLX to WATCHMAN FLX Pro[b]	
Polyvinylidene difluoride-hexafluoropropylene (PVDF-HFP) coating applied to finished implant	Designed to improve device hemocompatibility by lessening severity of the acute foreign body response to the implant and to encourage endothelialization
Proximal radiopaque markers at the plane of maximum diameter of the implant	Intended to assist with visibility, deployment, and device positioning
Sealing of the distal hypotube-to-core-wire segment of the core wire assembly	Reduce the amount of air required to be removed from the delivery system during preparation
Redesigned deployment knob	For improved ergonomics and product identification
40mm implant size	Additional size option
Updated packaging tray	To accommodate the new deployment knob design

a: Additional features of the WATCHMAN FLX device as compared to the predicate WATCHMAN™ device
b: Additional features of the WATCHMAN FLX Pro device as compared to the WATCHMAN FLX Device
Abbreviation: LAA=left atrial appendage

Additionally, WATCHMAN FLX Pro materials which come into contact with the human body are listed below in Table 5.2-3.

Table 5.2-3: WATCHMAN FLX Pro – Materials

Device Component	Materials Coming Into Contact With the Human Body
Deployment Hypotube	304 Stainless Steel
Hypotube Seal	Trogamid
Y Adapter Retainer and Stopcock Core	Polyoxymethylene (Delrin)
Y Adapter Seal	Silicone
Y Adapter Assembly	Polycarbonate has Bisphenol A (0.005%)
2-way Stopcock Body	• Polycarbonate • Polycarbonate has Bisphenol A (.0017%) • Polyoxymethylene (Delrin) • Colorant Clariant MFG#MO0M664823 White PMS#9061C Acetal EC, IBC, L (2.2%) • DOW Corning Silicone Fluid, 360 Medical Grade (.062%)
Threaded Core Wire	Nitinol (nickel titanium alloy)
Core Wire Cap	Titanium
Core Wire Jacket and Delivery Sheath Tubing, Reflow Extrusion, Hub	PEBAX
Hub	White Colorant (Brenntag Titanium Dioxide 325) (1.5%) PEBAX also has White Colorant (CSRM083 C.I. Pigment White 6) (1.5%)
Delivery Sheath PEBAX	Heat stabilizer (.25%) and light stabilizer (.25%)
Delivery Sheath Liner and Y-Adapter Backup Ring	Polytetrafluoroethylene (PTFE)
WATCHMAN FLX Pro LAA Closure Device	Nitinol (nickel titanium alloy), PET, Titanium – Grade 2, CI Pigment White 6 Titanium Dioxide (0.3%), Tantalum, PVDF-HFP, Acetone, Dimethyl sulfoxide (DMSO)

5.3. *Overview of the WATCHMAN Access System (Access Sheath and Dilator)*

Commercially available access systems to use with WATCHMAN FLX Pro include the WATCHMAN® Access System and the WATCHMAN™ TruSeal™ Access System. They all have a dilator and access sheath, which are used to gain access to the LAA once initial transseptal entrance into the left atrium has been established. The distal end of the access sheath is available in multiple curve styles for coaxial placement in the LAA. The distal tip contains a marker band for in situ visualization.

Once the access sheath is positioned in the left atrium and the dilator has been removed, the sheath serves as a conduit for the WATCHMAN FLX Pro Delivery System. The delivery system is introduced into the access sheath and the components snap together to act as one during device implantation. Additional product information can be found in the associated Access System IFUs.

The commercially available access systems are required to be used in the study but are not themselves subject of the clinical investigation. They are commercially-labeled and will be managed per each institution's standard practice.

6. Study Objectives and Endpoints

6.1. *Study Objectives*

The primary objective of this study is to measure device tissue coverage post-implantation of WATCHMAN FLX™ Pro using the serial advanced imaging modalities of cardiac CT and TEE and assess its relationship, if any, to clinical events.

Table 6.1-1 provides an overview of the study objectives and endpoints and a rationale for the specific endpoints. Additional information on endpoints is provided in Section **6.2**.

Table 6.1-1: Overview of Objectives and Endpoints

Objective	Endpoint	Rationale for Endpoint
Primary Endpoint	Device surface morphology (inclusive of tissue coverage) post implant procedure as assessed over time using the serial advanced imaging modalities of cardiac computed tomography and transesophageal echocardiography	Imaging surveillance at follow-up allows assessment of device tissue coverage, peri-device leaks, and device-related thrombus, which may be associated with late thromboembolic events. Data are evaluated by an independent core laboratory.
Additional Measurements of Safety and Effectiveness		
Evaluate safety of the implant and the procedure	Safety measures at discharge, 14 days, 45 days, 3 months, and 12 months post implant procedure	Safety assessments, including early cardiac safety, with events adjudicated by an independent Clinical Events Committee
Evaluate effectiveness of the implant	Imaging and biochemical marker analyses at 14 days, 45 days, and 3 months post implant procedure	Identify any correlations of biochemical markers with morphological findings from imaging assessments of the device surface

6.2. *Study Endpoints*

Prespecified endpoints are listed below. Definitions can be found in **Table 25.2-1**.

6.2.1. Primary Endpoint

The primary endpoint is device surface morphology (inclusive of tissue coverage) as assessed over 14 days, 45 days and 3 months post implant procedure using the serial advanced imaging modalities of cardiac computed tomography (CT) and transesophageal echocardiography (TEE).

6.2.2. Additional Measurements

Additional endpoint measurements will be collected peri- and post-procedure, predischarge, and at 14 days, 45 days, 3 months, and 12 months after the implant procedure, unless specified otherwise below.

- Safety endpoints (adjudicated by an Independent Clinical Events Committee [CEC]):
  - All-cause mortality (cardiovascular/unknown and non-cardiovascular)
  - Stroke (disabling and non-disabling; ischemic and hemorrhagic)

    Note 1: For subjects diagnosed with a neurological event (e.g., stroke, transient ischemic attack [TIA]), mRS and NIHSS should be performed after the event. It is recommended that the subject be contacted regarding mRS assessment at 90±14 days following any suspected stroke; the simplified mRS questionnaire[38] may be used for this follow-up assessment. It is recommended that imaging be performed after the event to screen for device related thrombus (DRT). If performed, imaging results should be sent to the core laboratory.
  - Systemic embolism
  - Bleeding: International Society on Thrombosis and Haemostasis (ISTH) major and non-major clinically significant[39,40]
    - Procedural bleeding (≤7 days post-procedure)
    - Non-procedural bleeding (>7 days post-procedure)
  - Pericardial effusion/tamponade requiring pericardiocentesis or surgery
- Device Success: defined as implantation of a WATCHMAN FLX Pro device without in-hospital mortality.
- Assessments by serial imaging modalities (CT and TEE, optional cardiac magnetic resonance imaging [MRI]) at 14 days, 45 days, and 3 months (TEE optional at 3 months if there is no leak at 45 days). Data will be evaluated by an independent core lab.
  - Device seal at 45 days post implant procedure (see **Note 2** and **Note 3**)
  - Device-related thrombus (including hypoattenuated thickening [HAT] per CT analysis)
- **Note 2:** Results are classified as no leak, leak >0 and ≤5mm, or leak >5mm
  Note 3: TEE should be performed at 12 months if the 3-month TEE assessment suggests a leak > 5mm or the 3-month CT assessment suggests a leak > 3mm; results must be sent to the core laboratory.

- 4D MRI flow analysis (if available) of the left atrium (LA) and LAA before (14 days prior to the implant procedure) and serially after device implant (at 14 days, 45 days, and 3 months); data will be evaluated by an independent core lab.
- Changes compared to baseline in measures of biochemical markers including coagulation, platelet and endothelial activation and inflammation over time post implant procedure (at 14 days, 45 days, and 3 months); correlations with morphological findings from imaging assessment of the device surface will be examined.

7. Study Design

WATCHMAN FLX™ Pro CT is a prospective, single-arm, single-center, premarket investigation to assess device tissue coverage in subjects with non-valvular atrial fibrillation (AF) who receive a WATCHMAN FLX Pro device to reduce the risk of stroke. Serial advanced imaging modalities such as CT and TEE will be used. A core laboratory will independently assess select results.

7.1. *Scale and Duration*

Up to 50 subjects in whom placement of a WATCHMAN device is attempted will be enrolled in WATCHMAN FLX Pro CT in 1 investigational center in western Europe. Eligibility for the study is determined per standard of care. Any additional study specific testing to verify inclusion/exclusion criteria (see Section **8** below) must be done after the ICF is signed.

All subjects will be assessed at baseline and post-implant on the procedure day, at predischarge, and at 14 days, 45 days, 3 months, and 12 months post implant procedure. Follow-up will include in-person clinical assessments at all time points except 12 months (in person [preferred] or by telephone). Follow-up imaging assessments will occur at 14 days, 45 days, and 3 months. Additional imaging may be done at 12 months if required based on imaging data obtained at earlier time points.

Subjects who are enrolled but not implanted with a WATCHMAN FLX Pro device will be followed for safety through 12 months after the initial attempted implant procedure by telephone or review of clinical files but will not undergo imaging assessments or evaluation of biochemical markers (including measures of coagulation, platelet and endothelial activation and inflammation). **Figure 7.1-1** provides an overview of the study design.

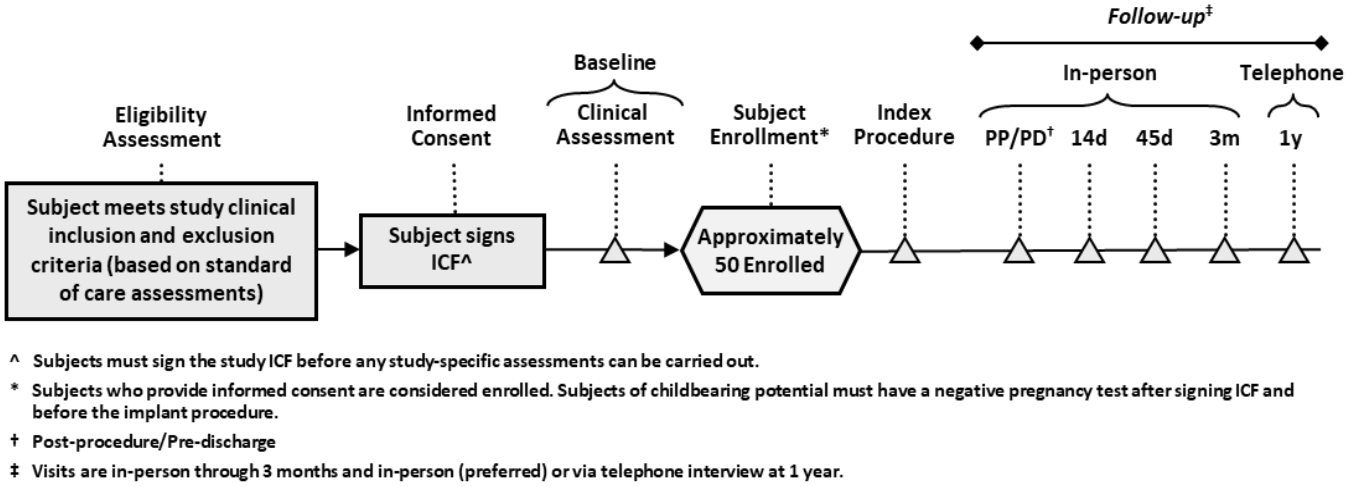


Figure 7.1-1: WATCHMAN FLX Pro CT Study Design Overview

Eligibility for the study is determined per standard of care. Any additional study specific testing to verify inclusion/exclusion criteria must be done after the ICF is signed.
Abbreviations: CT=computed tomography; ICF=Informed Consent Form

Due to the addition of 25 more patients to the initial 25 patients implanted, the enrollment period will be extended to minimally 15 months; therefore, the total study duration from first subject enrolled to last subject follow-up is estimated to be at least 28 months.

The WATCHMAN FLX Pro CT study will be registered at www.ClinicalTrials.gov prior to enrollment of the first subject (see Section **22.1**).

7.2. *Treatment Assignment*

Subjects who are identified by the investigators as having met all the inclusion and none of the exclusion criteria (see below **Table 8.2-1** and **Table 8.3-1**, respectively) may be treated with the WATCHMAN FLX Pro device.

7.3. *Justification for the Study Design*

In order to support the stated objectives of this study (see Section **6.1**) while also limiting the potential exposure of study subjects to risk, approximately 50 subjects will be enrolled at 1 center. Device implantation will be done according to current indications and device labelling as described in the device IFU. Safety and effectiveness results will be reported on all enrolled subjects (see Section **18** for information on safety reporting). All subjects will be followed for up to 12 months post implant procedure. To decrease the risk of thrombotic or thromboembolic complications, subjects will be treated with single antiplatelet therapy (SAPT) for at least 3 months following WATCHMAN FLX Pro implantation.

8. Subject Selection

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.

Vulnerable subjects (see **Table 25.2-1** for the definition of vulnerable subject) will not be enrolled in the WATCHMAN FLX Pro CT study.

8.1. *Study Population and Eligibility*

8.2. *Inclusion Criteria*

Subjects who meet all of the criteria in **Table 8.2-1** may be given consideration for inclusion in this clinical investigation, provided no exclusion criterion (see Section **8.3**) is met.

Table 8.2-1: Inclusion Criteria

IC1.	Subject is of legal age to participate in the study per the laws of their respective geography.
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) and who has a relative or absolute contraindication to anticoagulation.
IC3.	Subject is deemed suitable for the protocol-defined pharmacologic regimen.
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*

Exclusion criteria are shown in **Table 8.3-1**. Subjects who meet any one of these criteria will be excluded.

Table 8.3-1: Exclusion Criteria

EC1.	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.
EC2.	Subject has eGFR <30 mL/min (chronic kidney disease stage IV or stage V).
EC3.	Subject is contraindicated for TEE.

Table 8.3-1: Exclusion Criteria

EC4.	Subject requires long-term anticoagulation therapy for reasons other than AF-related stroke risk reduction (e.g., due to an underlying hypercoagulable state).
EC5.	Subject had or is planning to have any cardiac or non-cardiac intervention or surgical procedure within 30 days prior to or 60 days after implant (including, but not limited to, cardioversion, percutaneous coronary intervention, cardiac ablation, cataract surgery, etc.).
EC6.	Subject had a prior stroke (of any cause, whether ischemic or hemorrhagic) or transient ischemic attack (TIA) within the 30 days prior to enrollment.
EC7.	Subject had a prior major bleeding event per ISTH definitions within the 30 days prior to enrollment. Lack of resolution of related clinical sequelae or planned and pending interventions to resolve bleeding/bleeding source are a further exclusion regardless of timing of the bleeding event.
EC8.	Subject has an active bleed.
EC9.	Subject has a reversible cause for AF or has transient AF.
EC10.	Subject has no LAA or the LAA is surgically ligated.
EC11.	Subject has had a myocardial infarction (MI) documented in the clinical record as either a non-ST elevation MI (NSTEMI) or as an ST-elevation MI (STEMI), with or without intervention, within 30 days prior to enrollment.
EC12.	Subject has a history of atrial septal repair or has an atrial septal defect/patent foramen ovale (ASD/PFO) device.
EC13.	Subject has a known contraindication to percutaneous catheterization procedure.
EC14.	Subject has a cardiac tumor.
EC15.	Subject has signs/symptoms of acute or chronic pericarditis.
EC16.	Subject has an active infection.
EC17.	There is evidence of tamponade physiology.
EC18.	Subject has New York Heart Association Class IV congestive heart failure at the time of enrollment.
EC19.	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).
EC20.	Subject has a documented life expectancy of less than 6 months.

Abbreviations: AF=atrial fibrillation; EC=exclusion criterion; eGFR=estimated glomerular filtration rate; ISTH=International Society on Thrombosis and Haemostasis; LAA=left atrial appendage; MRI=magnetic resonance imaging; TEE=transesophageal echocardiography

9. Subject Accountability

9.1. *Point of Enrollment*

A subject is considered enrolled in the study when the subject or the subject's legally authorized representative signs an ICF approved by the IEC. No study-specific tests, procedures, etc. can take place until the ICF is signed. A subject who is determined to not

meet study specific clinical eligibility criteria after signing consent will be considered a screen failure (see **Table 9.4-1**) and will not count towards the enrollment ceiling.

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*

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

A subject will be considered lost to follow-up if he or she fails to be available for 2 consecutive scheduled visits without due cause 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.
- Before a subject is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts will be documented in the subject's medical record or study file.
- Should the subject continue to be unreachable, 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 9.4-1 describes subject status/classification and associated forms.

Table 9.4-1: Subject Status and Classification

Classification	Description
Screen Failure	A subject who signs an ICF but does not meet clinical eligibility criteria 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 and the following forms must be completed for all information collected prior to determining the subject's ineligibility. • Baseline forms such as, but not limited to, ICF, baseline information and other related forms • Adverse Event form(s) for any reportable event, as defined in Section **18**, for any adverse event that occurs after signing the ICF, up to the point of subject exit
Attempt	A subject who signs an ICF, meets eligibility criteria, and has had a WATCHMAN Access Sheath inserted to implant the device, but eventually does not receive a WATCHMAN FLX Pro device will 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 count towards the enrolment ceiling and will be used for analyses of the 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 • First 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 is successfully implanted with the WATCHMAN FLX Pro device will be classified as "Implant." Successfully implanted subjects are those defined as having device success, where the device has been deployed and implanted in the correct position. These 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 10.1-1** below) has occurred. All enrolled subjects will be evaluated clinically post-implant on the procedure day, at predischarge, at 14 days, 45 days, 3 months, and 12 months post implant procedure (preferably all in-person visits; see **Table 10.1-1** for additional information).

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, with the consent of the subject provided for collection of this data.

10. Study Methods

10.1. *Data Collection*

This section lists the data needed to fulfill the objectives of this clinical study. Boston Scientific Corporation considers data collected from clinical trial subjects to be personal data (see definitions of different data categories in **Table 25.2-1**) and compliance with privacy and data protection laws and regulations (for example, the General Data Protection Regulation [GDPR]) to be critically important. Data collection for this clinical study has been carefully considered to comply with data privacy laws.

The data collection schedule is provided in **Table 10.1-1** and summarized diagrammatically in

Figure 10.1-1. Additional information, including recommended post-procedure medical therapy, is provided in Section **10.2** through Section **10.10**. 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 in **Table** 10.1-1. Required follow-up assessments and visits not completed will be considered missed visits and recorded as protocol deviations. Visits completed outside follow-up windows 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.

Table 10.1-1: WATCHMAN FLX Pro CT Study Event Schedule

Assessment	Baseline	Implant Procedure	Predischarge	14 Days [a] (± 3 Days)	45 Days [a] (± 15 Days)	3 Months [a] (90 ± 30 Days)	12 Months [a] (365 ± 30 Days)
Signed Informed Consent Form (date)	X	–	–	–	–	–	–
Demographics	X	–	–	–	–	–	–
Pregnancy Test[j]	X[j]						
Medical history and inclusion/exclusion criteria	X	–	–	–	–	–	–
Physical assessment	X	–	–	–	X	X	O
Risk factor assessments[b] (HAS-BLED and CHA_2DS_2-VASc scores)	X	–	–	–	–	–	–
TEE of LAA[c]	X[c]	–	–	X	X	X[c]	O[d]
CT of LAA[c]	X[c]	–	–	X	X	X	O
MRI of LAA[e]	O	–	–	O	O	O	O
Labs – biochemical markers[f]	X	–	–	X	X	X	O
NIHSS Stroke Scale[g]	X	–	–	–	–	–	–
Modified Rankin Scale score[g]	X	–	–	–	–	–	–
Procedural ICE[h]	–	X	–	–	–	–	–
Medications	X	X	X	X	X	X	X
SAE, ADE, SADE, USADE, procedure-related AE and device deficiencies[i]	–	X	X	X	X	X	X

Note 1: X = should be performed; O=optional (unless required based on other data); – = not required
Baseline assessments should be done within 30 days unless specified otherwise in the footnotes below. Eligibility for the study is determined per standard of care. Any additional study specific testing to verify inclusion/exclusion criteria must be done after the ICF is signed.

a: All follow-up dates will be calculated from the date of the (attempted) implant procedure. Subjects are considered enrolled in the study when the subject or the subject's legally authorized representative signs an ICF approved by the Independent Ethics Committee. Clinical follow-up is in-person at 14 days, 45 days, and 3 months. Follow-up at 12 months is in-person (preferred) or by telephone (unless an in-person assessment is required based on other data). Subjects who are enrolled but do not have a WATCHMAN FLX™ Pro LAA Closure Device implanted in the correct position will be followed for safety through 12 months after the initial attempted implant procedure by telephone or review of clinical files but will not undergo imaging assessments or evaluation of biochemical markers.

b: Risk factor assessments include HAS-BLED and CHA_2DS_2-VASc scores.

c: Either TEE or CT must be done within 14 days prior to the implant procedure (baseline assessment) following the core laboratory guidelines (see Section **12.3**). CT at 14 days, 45 days, and 3 months are required for all subjects who have a WATCHMAN FLX™ Pro LAA Closure Device implanted in the correct position and should be performed per the core lab guidelines. TEE is required at 14 days, 45 days and optional at 3 months if there is no leak at 45 days, for all subjects who have a WATCHMAN FLX™ Pro LAA Closure Device implanted in the correct position and should be performed per the core lab guidelines. Results must be sent to the core laboratory for independent analysis (see Section **12.3**).

d: Repeat TEE should be done at 12 months if the 3-month TEE assessment suggests a leak > 5mm or the 3-month CT assessment suggests a leak > 3mm; results must be sent to the core laboratory.

e: MRI imaging assessments are optional. If MRI assessment is done, core laboratory guidelines should be followed. Results must be sent to the core laboratory for independent analysis (see Section **12.3**).

f: Labs include biochemical markers including measures of coagulation, platelet and endothelial activation and inflammation. At baseline, these labs should be obtained within 30 days prior to the implant procedure. Baseline serum creatinine is also required and should be obtained within 30 days prior to consent.

g: Baseline neurological assessments should be done within 30 days prior to the implant procedure. For subjects diagnosed with a neurological event (e.g., stroke, TIA), mRS and NIHSS should be performed after the event. It is recommended that the subject be contacted regarding an mRS assessment at 90±14 days following any suspected stroke; the simplified mRS questionnaire may be used for this follow-up assessment and may be collected by telephone.

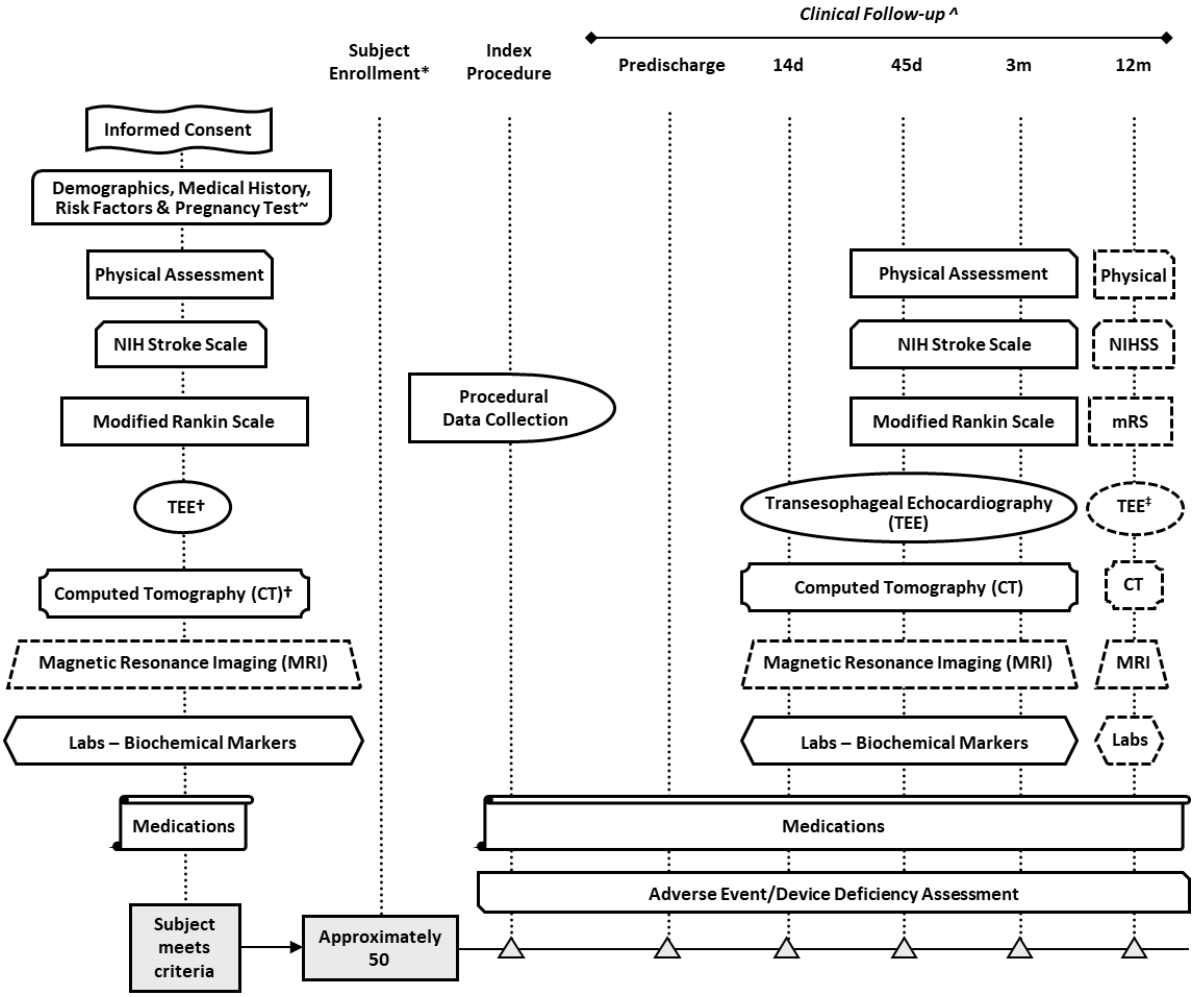
Note 2: If a subject has a stroke or other thromboembolic event, work-up should occur as per local standard of care. It is recommended that imaging be performed to screen for DRT. If performed, imaging results should be sent to the Core Laboratory.

h: Procedural ICE data should be sent to the Core Laboratory.

i: Safety events will be monitored and reported to Boston Scientific Corporation from the time of enrollment through 12-month follow-up. Please refer to Section **18.1** for a list of events to be adjudicated by the CEC through completion of a subject's participation in the study and **Table 25.2-1** for definitions of these events, which specify data required for CEC adjudication. Reporting of device deficiencies will follow applicable regional safety surveillance requirements.

j: Required for subjects of childbearing potential and subject must have a negative pregnancy test after signing the ICF and prior to the implant procedure.

Abbreviations: ADE=adverse device effect; AE=adverse event; CEC=Clinical Events Committee; CHA_2DS_2-VASc=congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/TIA, vascular disease, age 65–74 years, sex category; CT=computed tomography; DRT=device related thrombus; HAS-BLED=hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly, drugs/alcohol concomitantly; ICE=intracardiac echocardiography; ICF=Informed Consent Form; LAA=left atrial appendage; MRI=magnetic resonance imaging; mRS=modified Rankin Scale; NIHSS=National Institutes of Health Stroke Scale; SADE=serious adverse device effect; SAE=serious adverse event; TEE=transesophageal echocardiography; TIA=transient ischemic attack; USADE=unanticipated serious adverse device effect



*** A subject is considered enrolled in the study when the subject or the subject's legally authorized representative signs an ICF approved by the IEC.**

~ A subject of childbearing age must have a negative pregnancy test after signing the ICF to be enrolled in the study

^ Clinical follow-up is in-person at 14 days, 45 days, and 3 months and in-person (preferred) or by telephone at 12 months.

† Baseline CT or TEE must be done within 14 days prior to the index procedure.

‡ Repeat TEE should be done at 12 months if the 3-month TEE suggests a leak > 5mm or the 3-month CT assessment suggests a leak > 3mm.

Figure 10.1-1: WATCHMAN FLX Pro CT Study Event Schedule Summary Diagram

Up to 50 subjects will be enrolled. Dashed line indicates the assessment is optional unless required based on other data. Eligibility for the study is determined per standard of care. Any additional study specific testing to verify inclusion/exclusion criteria must be done after the Informed Consent Form is signed.
Please see **Table 10.1-1** for additional information.

10.2. *Study Candidate Screening*

Investigators are responsible for screening all subjects and selecting those who are appropriate for study inclusion as per the clinical IFU. The subjects selected for participation should be from the Investigator's general patient population. Pregnant women and women who plan to become pregnant during the 12 month follow up period are excluded from this study. A woman of childbearing potential must have a negative pregnancy test after signing the consent form and prior to the implant procedure. Women of childbearing potential are required to use highly effective contraceptives during the course of the study (through 12 month follow up visit).

Highly effective contraceptive methods (less than 1% failure rate) include the following:

- Hormonal contraception:
  - birth control pills, ring, or patch that are combined estrogen and progestogen
  - birth control pills, injection, or implant that contains progestogen only
- Intrauterine device (IUD, birth control implant)
- Intrauterine hormone-releasing system (IUS, birth control implant)
- Bilateral tubal occlusion (tubes tied on both sides)
- Vasectomized partner with medical confirmation of success
- True sexual abstinence is acceptable if this is consistent with your preferred, usual, lifestyle. Periodic abstinence is not an acceptable method of contraception.

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

The WATCHMAN FLX Pro CT Study will include subjects presenting with documented non-valvular atrial fibrillation who are clinically indicated for a WATCHMAN FLX Pro device (see Section **8.2)**. Because AF prevalence is age-dependent, with a frequency exceeding 15% among individuals 80 years or older[2], women are well represented in LAAO studies. The inclusion and exclusion criteria are not expected to have a negative effect on recruitment or retention of subjects.

All efforts will be made to minimize attrition (see Section **9.3**). Investigators are encouraged to enroll subjects who are willing to comply with the follow-up requirements of the study. If a visit is missed, the center should attempt to contact the subject to reschedule the missed visit and counsel the subject on the importance of maintaining the assigned visit schedule.

10.3. *Subject Informed Consent*

Written informed consent (see Section **19**) must be obtained for all qualified subjects who are potential study candidates prior to the subject's implant procedure.

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. If the subject agrees to participate, the IEC-approved ICF must be signed and personally dated by the subject or his/her legally authorized representative. The Investigator/designee must sign the ICF prior to subject enrollment. Any additional persons required by the center's IEC to sign the ICF must also comply.

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.

10.4. *Baseline Assessments*

The following assessments must be completed within 30 days prior to the implant procedure, unless otherwise specified below. The study electronic case report forms (eCRFs) identify the specific data points to be collected.

- Confirmation of eligibility criteria and contraindications per the clinical IFU
- Clinical assessments
  - Demographics, including age at time of consent and sex
  - Medical and cardiac history; includes cardiovascular diseases, AF type (paroxysmal, persistent, permanent), prior history of stroke/transient ischemic attack (TIA), previous cardiac procedures, history of bleeding and location, eligibility for oral anticoagulation, indication for LAA occlusion
  - Physical assessment
  - Risk factor assessments, including HAS-BLED and CHA2DS2-VASc scores[41]
  - Current antiplatelet, anticoagulation, and other cardiovascular medications
  - mRS score and NIHSS score

    Note 1: Neurological status as determined by the mRS score should also be determined following any suspected stroke; it is recommended that the subject be contacted regarding an mRS assessment at 90±14 days post-stroke; the simplified mRS questionnaire[38] may be used for this follow-up assessment and may be collected by telephone.

- Approximately 15 mL of blood will be drawn for analysis which will include baseline serum creatinine (may be obtained up to 30 days prior to consent) and biochemical markers including measures of coagulation, platelet and endothelial activation and inflammation. The following is the list of blood analyses performed:
  - Platelet count
  - Mean platelet volume
  - Immature platelet fraction
  - Plasma selectin
  - INR
  - Activated partial thromboplastin time
  - Von Willebrand factor
  - D-dimer
  - Prothrombin Fragment 1+2
  - Hgb
  - Brain natriuretic peptide
  - C-reactive protein
  - Creatinine
  - eGFR

- Imaging assessments
  - Either CT or TEE assessment of the LAA must be carried out within 14 days prior to the implant procedure to confirm LAA size and to document that eligibility criteria have been met. Results must be sent to the core lab. This preprocedural imaging assesses appendage anatomy and device sizing and excludes the presence of a LAA thrombus. Suitability for attempted device implantation will be assessed as follows.
    - Using multiple imaging planes, LAA size/shape, number of lobes in the LAA, and location of lobes to ostium will be determined.
    - Absence of thrombus will be confirmed. If an intracardiac thrombus is visualized, device implantation will not be attempted. Re-assessment may be scheduled per the physician's discretion.
    - Measurements of the LAA ostium width and LAA depth will be recorded. The measured maximum LAA ostium width must be ≥ 14.0 mm and ≤ 36 mm to accommodate the available WATCHMAN FLX Pro device sizes.
  - Cardiac MRI assessment (including 4D cardiac MRI flow analysis of the LA and LAA) is optional but if performed, the results must be sent to the core lab.
  - All protocol required pre-procedural imaging will be performed by trained individuals and in accordance with core lab instructions (see Section **12.3**). Copies of the imaging results will be sent to the core lab for independent analysis. Additionally, copies of all LAA imaging will be saved to disk at the center and available to the sponsor upon request. The center and subject identification number should be clearly identified on the disks.

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 but should be the same as the intended post-procedure antiplatelet therapy.
- Patients that are actively treated by SAPT pre-procedure should not receive a loading dose
- Anticoagulant therapy (e.g., unfractionated heparin) must be administered per local standard of care during the implant procedure, with a recommended target activated clotting time (ACT) of ≥250 seconds during the implantation 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. *Implant 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 clinical IFU and the WATCHMAN® Access System or the WATCHMAN™ TruSeal™ Access System IFU for detailed instructions regarding device use.

The following information will be collected in the eCRF during the procedure. Additional data to be collected may be outlined in the eCRF.

- Date of procedure
- WATCHMAN FLX Pro LAA Closure Device size used
- Commercially available WATCHMAN Access System or the WATCHMAN™ TruSeal™ Access System used
- Procedural ICE data with results sent to the core laboratory
- Medications
- Adverse event assessment (see Section **18**)

10.7. *Predischarge*

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 complete safety event assessment must be done. The study eCRFs identify the specific data points to be collected. 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 with associated treatment.

Note 1: For subjects diagnosed with a neurological event (e.g., stroke, TIA), mRS and NIHSS should be performed after the event. It is recommended that the subject be contacted regarding an mRS assessment at 90±14 days post-neurological event; the simplified mRS questionnaire[38] may be used for this follow-up assessment and may be collected by telephone. It is recommended that imaging be performed after the event to screen for DRT. If performed, imaging results should be sent to the core laboratory.

Antiplatelet therapy post implant procedure is recommended to reduce the risk of thrombotic or thromboembolic complications if there are no contraindications to these medications. Subjects must be treated with single antiplatelet therapy (SAPT; aspirin or $P2Y_{12}$ inhibitor) for at least 3 months 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*

All subjects successfully implanted with a WATCHMAN FLX Pro device will be evaluated at 14 days, 45 days, 3 months, and 12 months post implant procedure. Subjects who are enrolled but not implanted with a WATCHMAN FLX Pro device in the correct position will be followed for safety through 12 months after the initial attempted implant procedure by telephone or review of clinical files but will not undergo imaging assessments or evaluation of biochemical markers including measures of coagulation, platelet and endothelial activation and inflammation.

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. 14-Day Follow-up (14 Days ±3 Days)

All enrolled subjects will be evaluated 14 days after the implant procedure. The study eCRFs identify the specific data points to be collected as listed below.

- Complete safety event assessment, including any SAE, ADE, SADE, USADE, device deficiency with associated treatment, and any CEC event regardless of seriousness and device relationship.

  Note 1: For subjects diagnosed with a neurological event (e.g., stroke, TIA), mRS and NIHSS should be performed after the event. It is recommended that the subject be contacted regarding an mRS assessment at 90±14 days following any suspected stroke; the simplified mRS questionnaire[38] may be used for this follow-up assessment and may be collected by telephone. It is also recommended that imaging be performed to screen for DRT. If performed, imaging results should be sent to the core laboratory.

- All antiplatelet medications, which should be administered in accordance with local standard of care. Subjects must be treated with SAPT (aspirin or $P2Y_{12}$ inhibitor) for at least 3 months following WATCHMAN FLX Pro implantation.
    - Approximately 15 mL of blood will be drawn for analysis of biochemical markers measures of coagulation, platelet and endothelial activation and inflammation. The following is the list of blood analyses performed:
        - Platelet count
        - Mean platelet volume
        - Immature platelet fraction
        - Plasma selectin
        - INR
        - Activated partial thromboplastin time
        - Von Willebrand factor
        - D-dimer
        - Prothrombin Fragment 1+2
        - Hgb
        - Brain natriuretic peptide
        - C-reactive protein
        - Creatinine
        - eGFR

- TEE is required for all subjects who have a WATCHMAN FLX™ Pro LAA Closure Device implanted in the correct position and should be performed per the core lab guidelines, including assessment of device seal and device surface morphology (inclusive of tissue coverage) post implant procedure. Results must be sent to the core lab for independent analysis.
- CT is required for all subjects who have a WATCHMAN FLX™ Pro LAA Closure Device implanted in the correct position and should be performed per the core lab guidelines, including assessment of device seal, device-related thrombus (including hypoattenuated thickening [HAT]) and device surface morphology (inclusive of tissue coverage) post implant procedure. Results must be sent to the core lab for independent analysis.
- Cardiac MRI assessment, including 4D cardiac MRI flow analysis of the LA and LAA, is optional but if performed, the results must be sent to the core lab for independent analysis.

Subjects who are enrolled but do not receive a WATCHMAN FLX Pro Device in the correct position during the implant procedure will be followed for safety through 12 months after the initial attempted implant procedure by telephone or review of clinical files but will not undergo imaging assessments or evaluation of biochemical markers including measures of coagulation, platelet and endothelial activation and inflammation.

10.8.2. 45-Day Follow-up (45±15 Days) and 3-Month Follow-up (90±30 Days)

All enrolled subjects will be evaluated 45 days and 3 months after the implant procedure. The study eCRFs identify the specific data points to be collected as listed below.

- Complete safety event assessment, including any SAE, ADE, SADE, USADE, device deficiency with associated treatment, and any CEC event regardless of seriousness and device relationship.

  Note 1: For subjects diagnosed with a neurological event (e.g., stroke, TIA), mRS and NIHSS should be performed after the event. It is recommended that the subject be contacted regarding an mRS assessment at 90±14 days following any suspected stroke; the simplified mRS questionnaire[38] may be used for this follow-up assessment and may be collected by telephone. It is also recommended that imaging be performed after the event to screen for DRT. If performed, imaging results should be sent to the core laboratory.

- All antiplatelet medications, which should be administered in accordance with local standard of care. Subjects must be treated with SAPT (aspirin or $P2Y_{12}$ inhibitor) for at least 3 months following WATCHMAN FLX Pro implantation.

- Physical assessment as per local standard of care

  - Approximately 15 mL of blood will be drawn for analysis of biochemical markers which will include measures of coagulation, platelet and endothelial activation and inflammation. The following is the list of blood analyses performed:
    - Platelet count
    - Mean platelet volume
    - Immature platelet fraction
    - Plasma selectin
    - INR
    - Activated partial thromboplastin time
    - Von Willebrand factor
    - D-dimer
    - Prothrombin Fragment 1+2
    - Hgb
    - Brain natriuretic peptide
    - C-reactive protein
    - Creatinine
    - eGFR

- TEE is required for all subjects who have a WATCHMAN FLX™ Pro LAA Closure Device implanted in the correct position at 45 days and should be performed per the core lab guidelines, including assessment of device seal and device surface morphology (inclusive of tissue coverage) post implant procedure. Results must be sent to the core lab for independent analysis.

- TEE is optional at 3 months for subjects who have a WATCHMAN FLX Pro LAA Closure Device implanted in the correct position if there is no leak at 45 days. However, if TEE is performed, results must be sent to the core lab for independent analysis.
- CT is required for all subjects who have a WATCHMAN FLX Pro LAA Closure Device implanted in the correct position and should be performed per the core lab guidelines, including assessment of device seal, device-related thrombus (including HAT) and device surface morphology (inclusive of tissue coverage) post implant procedure. Results must be sent to the core lab for independent analysis.
- Cardiac MRI assessment, including 4D cardiac MRI flow analysis of the LA and LAA, is optional but if performed, the results must be sent to the core lab for independent analysis.

Subjects who are enrolled but not implanted with a WATCHMAN FLX Pro Device in the correct position during the implant procedure will be followed for safety through 12 months after the initial attempted implant procedure by telephone or review of clinical files but will not undergo imaging assessments or evaluation of biochemical markers including measures of coagulation, platelet and endothelial activation and inflammation.

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

All subjects successfully implanted with a WATCHMAN FLX Pro Device will be evaluated at 12 months after the implant procedure. The study eCRFs identify the specific data points to be collected as listed below.

- Complete safety event assessment, including any SAE, ADE, SADE, USADE, device deficiency with associated treatment, and any CEC event regardless of seriousness and device relationship.

  Note 1: For subjects diagnosed with a neurological event (e.g., stroke, TIA), mRS and NIHSS should be performed after the event. It is recommended that the subject be contacted regarding an mRS assessment at 90±14 days following any suspected stroke; the simplified mRS questionnaire[38] may be used for this follow-up assessment and may be collected by telephone. It is also recommended that imaging be performed after the event to screen for DRT. If performed, imaging results should be sent to the core laboratory.
- All antiplatelet and other cardiovascular medications should be administered in accordance with local standard of care.

10.9. *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. Subjects who are enrolled but not implanted with a WATCHMAN FLX Pro Device in the correct position during the implant procedure will be followed for safety through 12 months after the initial attempted implant procedure by telephone or review of clinical files

but will not undergo imaging assessments or evaluation of biochemical markers including measures of coagulation, platelet and endothelial activation and inflammation.

10.10. *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 10.10-1**. Source documentation provided to the Sponsor for assessment/adjudication will be deidentified per local law and regulations.

Table 10.10-1: Source Documentation Requirements

Requirement	Disposition
Printed, optical, or electronic document containing source data. Examples may include but are not limited to the following: 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 25.2-1** for definitions of "source data" and "source document."

10.11. *Local Laboratory/Vendor Documentation*

Appropriate certifications and documentation records are required to be maintained at the investigative center for local laboratory/vendor work.

11. Statistical Considerations

11.1. *Endpoints*

11.1.1. Primary Endpoint

The primary endpoint, which is not a powered endpoint, is device surface morphology (inclusive of tissue coverage) post implant procedure as assessed over 14 days, 45 days, and 3 months post implant procedure using the serial advanced imaging modalities of cardiac computed tomography (CT) and transesophageal echocardiography (TEE). Descriptive statistics will be used to report outcomes for this non-powered primary endpoint. For this single-arm feasibility study with no formal pre-specified hypothesis, sample size estimates are not applicable. To support the stated objectives of this study, the study sample size has been limited to a maximum of 50 enrolled subjects.

11.1.2. Additional Procedural and Post-procedure Measurements

Procedural and post-procedure information will be collected as detailed in the clinical study schedule (**Table 10.1-1**) and will be summarized using descriptive statistics for continuous variables (e.g., mean, standard deviation, n, minimum, maximum) and frequency tables or proportions for discrete variables. The Kaplan-Meier product-limit method will be used to estimate rates for time-to-event endpoints. Adverse event and SAE rates will be reported.

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.

Statistical models that account for censored data will be employed in appropriate circumstances (e.g., for time-to-event outcomes).

11.2.1. Analysis Sets

Outcomes in WATCHMAN FLX Pro CT will be assessed on an ITT basis and an implanted basis. The ITT analysis set includes all subjects who sign an ICF (see Section **19**) approved by the IEC and who are enrolled in the study (see Section **9.1** for point of enrollment), whether or not the WATCHMAN FLX Pro device is implanted. The implanted analysis set includes ITT subjects who are successfully implanted with the study device in the correct position.

11.2.2. Control of Systematic Error/Bias

All subjects who have signed the ICF, met the inclusion/exclusion criteria (Section **8.2** and Section **8.3**) and are selected to receive a study device will be eligible for enrollment in the study (see Section **9.1** for point of enrollment). The selection of subjects will be made from the Investigator's usual case load. The study center's heart team assessments and imaging measurements before device placement will contribute to the determination of subject eligibility for the study.

To control for inter-observer variability, data from an independent core laboratory (see Section **12**) will be used for analysis at pre-specified time points. An independent CEC (see Section **20.1.1**) will adjudicate study endpoint related clinical events (see Section **6.2**).

11.2.3. Number of Subjects per Investigative Center

A single center may enroll up to 50 subjects.

11.2.4. Reporting Events

For all subjects who receive a study device, all events that occur from the time of enrollment (see Section **9.1**) will be reported. Subjects who are enrolled and have an attempted procedure but do not receive a study device will be followed for safety through 12 months after the initial attempted implant procedure by telephone or review of clinical files but will not undergo imaging assessments or evaluation of biochemical markers including measures of coagulation, platelet and endothelial activation and inflammation. For these subjects, events from the time of enrollment to 12 months post procedure will be reported.

For time-based clinical events, the cut-off for events for 14-day endpoints will be 14 days, for 45-day endpoints it will be 45 days, for 3-month endpoints it will be 90 days, and for 1-year endpoints it will be 365 days. For events at discharge or 7 days post-procedure, the cut-off for events will be the earlier of the date of discharge or 7 days post-procedure for each subject.

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). Study endpoints are listed in Section **6.2**. See Section **11.1** for a discussion on analysis of the primary endpoint and additional measurements.

Any changes to the planned statistical analyses made prior to performing the analyses will be documented in an amended statistical analysis plan approved before 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. Only personnel trained and authorized will have access to the system.

The clinical database will reside on a production server hosted by Medidata EDC System (New York, New York, USA). All changes made to the clinical data will be captured in an electronic audit trail and available for review by BSC 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 BSC 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 center for appropriate response. Center 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 are either "Hard Locked" or "Entry Locked." Once acceptance of the final study report or finalization of publications (as applicable) is received, final database storage and archiving activities can begin. When all closeout activities are completed, a request to the BSC Information Technology department is submitted to have the database locked or decommissioned and all database access revoked.

12.2. *Data Retention*

The Principal Investigator or his/her designee or investigational center will maintain all essential study documents and source documentation that support the data collected on the study subjects in compliance with applicable regulatory requirements. Documents must be retained for at least 2 years after the last approval of a marketing application or until at least 2 years have elapsed since the formal discontinuation of the clinical investigation of the product. These documents will be retained for a longer period of time by agreement with BSC or in compliance with other local regulations.

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. Centers are required to inform BSC in writing where paper or electronic files are maintained in case files are stored off site and are not readily available.

12.3. *Core Laboratory*

Echocardiography images, CT data, and MRI data (if applicable) will be evaluated by an independent core laboratory. Procedure guidelines for the required imaging assessments are provided by the core laboratory in the Manual of Operations. 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 BSC and the reviewing IEC of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency, and those deviations which affect the

scientific integrity of the clinical investigation. Such notice shall be given as soon as possible, but no later than 5 working days after the emergency occurred, or per prevailing local requirements, if sooner than 5 working days.

All deviations from the investigational plan, with the reason for the deviation and the date of occurrence, must be documented and reported to BSC using the EDC CRF. Centers may also be required to report deviations to the IEC and the regulatory authority, per local guidelines and government regulations.

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

The sponsor will not approve protocol waivers.

14. Device Accountability

14.1. *Investigationally-Labeled Test Devices*

This section applies to test devices being distributed with an investigational use indication on the device packaging. The principal investigator or an authorized designee shall do the following. See Section 5.1 and 5.2

For investigationally-labeed test devices, the principal investigator or an authorized designee shall do the following:

- Securely maintain and control access to these items to ensure they are used only in this clinical study and only per the protocol.
- Ensure the storage environment for these items is appropriate for maintaining conditions per the items' labeling (e.g., temperature, humidity, etc., as applicable)
- Maintain accurate and timely records, providing to the Sponsor upon request. Such records shall include the following content, at minimum.
    - Identification, quantity, and expiry date (if applicable) of each item received. Include batch number, serial number, or unique code, as applicable.
    - Date of receipt; open/use, and end disposition of each item and name of person(s) who performed those activities.
    - Subject identification/subject exposure to device and, if applicable, the date on which the item was returned/explanted from subject.
    - Reason for repair, disposal, or return to Sponsor (e.g., advisory/recall, sponsor request, other).
- Return or dispose of items as directed by Sponsor.
    - Complaint/deficiency related items should be returned whenever possible.

- Opened non-complaint/non-deficiency related items should be returned or disposed as directed by Sponsor.
- Unopened and reusable items should be returned to Sponsor or designee upon Sponsor request and in the condition in which they were provided, reasonable wear and tear excepted.

14.2. *Non-Test Medical Devices, Equipment, and Non-Medical Device Items*

Device under study (test device) accountability and investigational labeling do not apply to commercially-labeled medical devices and medical equipment that are not subject of the investigation nor to non-medical device items – see Sections **Error! Reference source not found.**. Unless otherwise directed by this protocol or other study-related materials, the tracking or special labeling of such items (if any) will be for logistical purposes only to facilitate study operations. These devices, equipment and items shall be managed per each institution's standard practice.

15. Compliance

15.1. *Statement of Compliance*

This clinical investigation is financed by the study sponsor. Before an investigational center can be considered "Authorized to Enroll," the investigational center 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 center and the investigator.

The WATCHMAN FLX Pro CT study will be conducted in accordance with the International Standard ISO 14155 Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice; relevant parts of the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practices (GCP); ethical principles that have their origins in the Declaration of Helsinki; and pertinent individual country/state/local laws and regulations. The study shall not begin until the required approval/favorable opinion from the IEC and/or regulatory authority has been obtained, if appropriate. Also, the study shall not begin prior to issuance of the center Authorization to Enroll, as provided by the sponsor. Any additional requirements imposed by the IEC or regulatory authority shall be followed, if appropriate.

15.2. *Investigator Responsibilities*

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

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

- Prior to beginning the study, sign the Clinical Study Agreement and comply with the Investigator responsibilities as described in such Agreement.
- Prior to beginning the study, sign the Investigator Brochure Signature Page and sign the Protocol Signature page documenting his/her agreement to conduct the study in accordance with the protocol.
- Provide his/her qualifications and experience to assume responsibility for the proper conduct of the study and that of key members of the site team through up-to-date curriculum vitae or other relevant documentation and disclose potential conflicts of interest, including financial, that may interfere with the conduct of the clinical study or interpretation of results.
- 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 BSC 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 BSC, per the protocol requirements, all reportable events.
- Report to the IEC and regulatory authorities any SAEs and device deficiencies that could have led to a SADE and potential USADE, if required by applicable laws or regulations or this protocol or by the IEC, and supply BSC with any additional requested information related to the safety reporting of a particular event.
- Maintain the device accountability records and control of the device, ensuring that the device under study (test device) is used only by authorized/designated users and in accordance with this protocol and instructions for use.
- Allow BSC and its representatives 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 IEC when performing auditing activities.

- Ensure that informed consent is obtained in accordance with applicable laws, this protocol, and local IEC 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 ICF.
- Inform the subject of the nature and possible cause of any adverse events experienced.
- Inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required.
- Provide the subject with well-defined procedures for possible emergency situations related to the clinical study, and make the necessary arrangements for emergency treatment, including decoding procedures for blinded/masked clinical investigations, as needed.
- Ensure that clinical medical records are clearly marked to indicate that the subject is enrolled in this clinical study.
- Ensure that, if appropriate, subjects enrolled in the clinical investigation are provided with some means of showing their participation in the clinical investigation, together with identification and compliance information for concomitant treatment measures (contact address and telephone numbers shall be provided).
- Inform, with the subject's approval or when required by national regulations, the subject's personal physician about the subject's participation in the clinical investigation.
- Make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from clinical investigation while fully respecting the subject's rights.
- Ensure that an adequate investigation center 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.

15.2.1. 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, so the delegate is competent to perform the tasks they have been delegated and adequate supervision of those to whom tasks are delegated. Where there is a sub-investigator at a center, the sub-investigator should not be delegated the primary supervisory responsibility for the center. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

15.3. *Independent Ethics Committee*

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

A copy of the written IEC and/or competent authority approval of the protocol (or permission to conduct the study) and ICF must be received by BSC 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 IEC before the changes are implemented in the study. All changes to the ICF will be IEC approved; a determination will be made regarding whether a new ICF needs to be obtained from subjects who provided consent using a previously approved ICF.

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

15.4. *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, a contract research organization (CRO) will have access to this information. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this study. Study data collected during this study may be used by BSC for the purposes of this study, publication, and to support future research and/or other business purposes, such as overseeing and improving the performance of its device, new medical research, and proposals for developing new medical products and procedures. All data used in the analysis and reporting of this study or shared with a third-party researcher will be without identifiable reference to specific subjects.

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

15.4.1. Role of Boston Scientific Corporation 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. Support may include HCP training (Section **15.4.2**), 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.

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

Boston Scientific personnel will not do the following.

- Practice medicine
- Provide medical diagnosis or treatment to subjects
- Discuss a subject's condition or treatment with a subject
- Independently collect critical study data (defined as primary or secondary endpoint data)
- Enter data in electronic data capture systems or on paper case report forms

15.4.2. Training

The Sponsor is responsible for providing investigators with the information and training on the device under study (test device) they need to conduct the study properly. The Sponsor is responsible for maintaining documentation of attendance at each of the training sessions provided.

The WATCHMAN FLX Training Plan meets the requirements of ISO 5840-3:2013. 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 physician training program.

15.5. *Insurance*

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

16. Monitoring

Monitoring will be performed during the study to assess continued compliance with the protocol and applicable regulations. In addition, the clinical research monitor verifies that study records are adequately maintained, that data are reported in a satisfactory manner with respect to timeliness, adequacy, and accuracy, and that the Principal Investigator continues to have sufficient staff and facilities to conduct the study safely and effectively. The Principal Investigator/institution guarantees direct access to original source documents by BSC personnel, their designees, and appropriate regulatory authorities.

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

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

17. Potential Risks and Benefits

Risks to clinical subjects associated with their participation in this clinical investigation, arising from the clinical procedures set out in the study protocol, have been identified from prior studies conducted by Boston Scientific Corporation and review of relevant literature.

Benefits to subjects anticipated to arise from the use of the device under study (test device) have also been identified. These clinical risks and benefits are summarized below, with an assessment of the balance of risks and benefits to subjects. Potential risks and benefits have been included in the study-specific template of the ICF provided to the study centers (see Section **19**).

17.1. *Anticipated Adverse Events*

Adverse events (in alphabetical order) potentially associated with the LAAO procedure (including, but not limited to, standard cardiac catheterization) as well as additional risks related to the use of the device under study (test device) Table **17.1-1** below. As a result of these complications, the subject may require medical, percutaneous, or surgical intervention. Such complications can be fatal.

As WATCHMAN FLX™ Pro is a device under study (test device), uncertainty remains over risks of experiencing some or all of the complications listed below. There may be risks that are unknown at this time.

Table 17.1-1: Risks Associated with Left Atrial Appendage Closure Device and Implantation Procedure

Air embolism
Airway trauma
Allergic reaction to medication, anesthetic, contrast media, or WATCHMAN implant materials
Altered mental status
Anemia requiring transfusion
Anesthesia risks
Angina
Anoxic encephalopathy
Arrhythmias
Atrial septal defect
Bruising, hematoma, or seroma near the catheter insertion site
Cardiac perforation
Chest pain/discomfort
Confusion post-procedure
Congestive heart failure
Contrast-related nephropathy
Cranial bleed
Death
Decreased hemoglobin
Deep vein thrombosis

Table 17.1-1: Risks Associated with Left Atrial Appendage Closure Device and Implantation Procedure

Device embolism
Device fracture
Device thrombosis
Edema
Embolism
Excessive bleeding
Fever
Fistula
Groin pain
Groin puncture bleed
Hematuria
Hemoptysis
Hypotension
Hypoxia
Improper wound healing
Inability to reposition, recapture, or retrieve the device
Infection/pneumonia
Interatrial septum thrombus
Intratracheal bleeding
Major bleeding requiring transfusion
Misplacement of the device/improper seal of the appendage/movement of device from appendage wall
Myocardial erosion
Myocardial infarction
Nausea
Oral bleeding
Pericardial effusion/tamponade
Pleural effusion
Prolonged bleeding from a laceration
Pseudoaneurysm
Pulmonary edema
Radiation injury
Renal failure
Respiratory insufficiency/failure
Stroke - Hemorrhagic
Stroke - Ischemic
Surgical removal of the device
Transesophageal echocardiography complications (e.g., throat pain, bleeding, esophageal trauma)
Thrombocytopenia
Thrombosis
Transient ischemic attack (TIA)
Valvular or vascular damage

Table 17.1-1: Risks Associated with Left Atrial Appendage Closure Device and Implantation Procedure

Vasovagal reactions

Note: Risks are listed in alphabetical order.
Source: WATCHMAN FLX™ Pro Clinical Instructions For Use

17.2. *Risks Associated with the Study Device*

Overall, there are no incremental risks expected with the device under study (test device) compared to similar devices on the market.

17.3. *Risks Associated with Participation in the Clinical Study*

Risks associated with 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 **Table 17.1-1** and in the ICF. There are no incremental risks associated with participation in this clinical study.

The baseline assessments in this study may include a CT scan. Protocol-required CT scans will occur at the 14-day, 45-day, and 3-month visits. Generally, the dose of radiation from 2 CT scans is about 20 mSv, or the equivalent of about an additional 10 years' worth of natural radiation. The benefits from the study should be weighed against the possible effects of radiation. The contrast dye used during the image acquisition can cause medical problems such as allergic reactions and increase the risk of worsening kidney function or failure.

17.4. *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. These risks may include the following.

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

17.5. *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 (see Section **20.1)** adjudication of specified events will support risk mitigation.

17.6. *Anticipated Benefits*

The potential benefit of implanting the WATCHMAN FLX Pro device is its expected ability to prevent thromboembolic events originating in the LAA. The WATCHMAN FLX Pro device may protect against ischemic stroke and systemic thromboembolism. In subjects implanted with the device, the elimination of long-term anticoagulation therapy may reduce bleeding complications associated with long-term anticoagulation, such as hemorrhagic stroke or gastrointestinal major bleeding events. There are also 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.

17.7. *Risk to Benefit Rationale*

Review of the aforementioned clinical benefits versus risks takes into account the known risks/benefits that have been identified from prior LAAO studies conducted by BSC and review of relevant literature. When used according to the IFU, all known risks associated with the procedure and the specific use of the study device are mitigated to acceptable limits comparable to existing LAAO devices.

18. Safety Reporting

18.1. *Reportable Events by Investigational Center to Boston Scientific*

After the informed consent is signed and the subject is considered enrolled in the study (as defined in the Subject Accountability section), whether prior to, during, or subsequent to the study procedure, the investigator must record, assess and report the following events to BSC:

- Serious adverse event (SAE) – see **Note 1** below
- Adverse event (AE) related to the WATCHMAN FLX Pro study device and/or WATCHMAN FLX Pro implant procedure

- Device deficiency
- Unanticipated serious adverse device effect (USADE)
- Adverse event related to the protocol-required testing (LAA imaging and blood draw)
- 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
- Strokes (regardless of cause) and TIAs regardless of relationship to the WATCHMAN FLX Pro device
- New findings/updates in relation to already reported events
- Serious (Public) Health Threats (SPHTs)

  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.

The investigator is also responsible for the recording, assessing and reporting of new and/or updated information in relation to already reported events in a timely fashion.

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

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

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

Underlying diseases and chronic conditions are not reported as AEs unless there is an increase in severity or frequency during the course of the investigation. Death should not be recorded as an AE but should only be reflected as an outcome of one (1) specific SAE (see **Table 18.2-1** for AE definitions) unless the cause of death is unknown.

The adverse events and/or safety endpoints (see endpoint definitions in **Table 25.2-1**) requiring adjudication by the independent CEC include the following.

- Mortality (all-cause: cardiovascular/unknown and non-cardiovascular)
- Stroke (disabling and non-disabling; ischemic and hemorrhagic)
- Systolic embolism
- Bleeding (ISTH major and non-major clinically significant; procedural and non-procedural)[39,40]

- Pericardial effusion/tamponade requiring pericardiocentesis or surgery
- Other events, at the discretion of Boston Scientific

Details on the CEC events and procedures are outlined in the CEC charter. Tests and images required to adjudicate these events are specified in the event definitions (see **Table 25.2-1**).

18.2. *Definitions and Classification*

Adverse event definitions are provided in **Table 18.2-1**. Administrative edits were made on the safety definitions from applicable regulations and guidance including (but not limited to) 21 CFR Part 812, ISO 14155 and EU MDR 2017/745/MDCG 2020-10/1 Guidance on Safety Reporting in Clinical Investigations for clarification purposes.

Table 18.2-1: Safety Definitions

Term	Definition
Adverse Event (AE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the study medical device and whether anticipated or unanticipated. **NOTE 1:** This includes events related to the study medical device or comparator. **NOTE 2:** This definition includes events related to the procedures involved. **NOTE 3:** For users or other persons, this definition is restricted to events related to the study medical device.
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.

Table 18.2-1: 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 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 1:** 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 1:** New adverse events occurring during the hospitalization are evaluated to determine if they prolonged hospitalization or meet another SAE criteria.

Table 18.2-1: Safety Definitions

Term	Definition
Procedural Definitions	• "Implant and Implant Procedure" refer to the procedure that involves the use of the device under study (test device) which is the subject of the clinical trial • "Study Procedure" refers to procedures required during the clinical trial, but do not involve the device under study (test device) • "Additional/Other Procedure" refers to procedures not specifically required by the protocol, but ones the subject may undergo as part of standard of care or in response to an adverse event

18.3. *Relationship to Study Device(s), (Device Under Study) and/or Study Procedure*

The Investigator must assess the relationship of the reportable AE to the WATCHMAN FLX Pro LAA Closure Device or study procedure. See criteria in **Table 18.3-1**.

Table 18.3-1: Criteria for Assessing Relationship of Study Device(s) (Device Under Study) 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 and/or an

Table 18.3-1: Criteria for Assessing Relationship of Study Device(s) (Device Under Study) or Procedure to Adverse Event

Classification	Description
	effect of another device, drug or treatment). Cases where relatedness cannot be assessed, or no information has been obtained should also be classified as possible.
Probably Related *Ref: MDCG 2020-10/1*	The relationship with the use of the study device, comparator, or the relationship with procedures seems relevant and/or the event cannot be reasonably explained by another cause.
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 and/or 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.

18.4. *Investigator Reporting Requirements*

The communication requirements for reporting to BSC are as shown in **Table 18.4-1**.

Table 18.4-1: Investigator Reporting Requirements

Event Classification	Communication Method	Communication Timeline (*EU MDR 2017/745, MDCG 2020-10/1*, MEDDEV 2.12/1 : GUIDELINES ON A MEDICAL DEVICE VIGILANCE SYSTEM)
Unanticipated Serious Adverse Device Effect (USADE)	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

Table 18.4-1: Investigator Reporting Requirements

Event Classification	**Communication Method**	**Communication Timeline** (*EU MDR 2017/745, MDCG 2020-10/1*, MEDDEV 2.12/1 : GUIDELINES ON A MEDICAL DEVICE VIGILANCE SYSTEM)
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• Upon request of Sponsor.
Serious Adverse Event (SAE) and CEC Events	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
Serious Adverse Device Effects (SADE) and Serious Adverse Events related to the protocol-required testing (LAA imaging)	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
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

Table 18.4-1: Investigator Reporting Requirements

Event Classification	**Communication Method**	**Communication Timeline** (*EU MDR 2017/745, MDCG 2020-10/1*, MEDDEV 2.12/1 : GUIDELINES ON A MEDICAL DEVICE VIGILANCE SYSTEM)
Adverse Event (AE) including Adverse Device Effects (ADE)	Complete AE eCRF page, which contains such information as date of AE, treatment of AE, resolution, assessment of seriousness and relationship to the device.	• ADE (or other key events of interest): in a timely manner but not later than 30 business days after becoming aware of the information • AE: in a timely manner (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
Serious Public Health Threat (SPHT)	Complete applicable CRF fields/forms with all available new and updated information.	• Immediately but not later than **2 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.	• When documentation is available

Abbreviations: AE=adverse event; CEC=Clinical Events Committee; eCRF=electronic case report form; LAA=left atrial appendage

18.5. *Device Deficiencies*

Device deficiencies for study devices (WATCHMAN FLX Pro LAA Closure Device preloaded on the WATCHMAN FLX Pro Delivery System) will be documented and reported to BSC using the Device Deficiency eCRF. If possible, the device(s) under study should be returned to BSC for analysis. Instructions for returning the device(s) will be provided on an individual basis. Device deficiencies should also be documented in the subject's source records.

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

Complaint reporting of any device deficiencies for any commercially available products used should be carried out using the manufacturer's processes.

18.6. *Reporting to Regulatory Authorities / IECs / Investigators*

Boston Scientific Corporation will notify all participating study centers if UADEs, SAEs, SADEs, or device under study (test device) deficiencies occur which imply a possible increase in the anticipated risk of the procedure or use of the device or if the occurrence of certain SAEs/SADEs requires changes to the protocol or the conduct of the study in order to further minimize the unanticipated risks.

Boston Scientific Corporation is responsible for reporting adverse event information to all participating Principal Investigators, IECs, and regulatory authorities, as applicable according to local reporting requirements.

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

Boston Scientific Corporation has established processes following ISO 14155:2020, Medical Device Regulation (EU) 2017/745, and MDCG 2020-10/1 reporting requirements.

The sponsor notifies the competent authority as described in the following sections:

<u>Conditions of Reporting:</u>

a) Any serious adverse event /device deficiency with a proven or reasonably foreseeable causal relationship with:
   - The medical device under investigation, a comparator device, or
   - The investigational procedure preceding it;
b) Any defect in a medical device which could have led to a serious adverse event in the absence of appropriate measures or intervention, or if the circumstances had been less favorable;
c) Any new development concerning an event referred to in points (a) and (b).

Notification begins from the time the clinical investigation is duly authorized, even if the first participant has not yet been enrolled in Denmark.

<u>Reporting Timelines from the Sponsor to the Competent Authority:</u>

- All reportable events and device deficiencies according to Article 80 MDR that have resulted in death or imminent risk of death, serious injury, or illness and that require prompt corrective action for participants / patients, users or others, or any new information related to these events:
  - Without delay (immediately) and no later than 2 calendar days from the day the sponsor became aware of the reportable event or new information regarding a previously reported event.

- All other reportable events and device deficiencies according to Article 80 MDR or any new information / update concerning them:
    - Without delay (immediately) and no later than 7 calendar days from the day the sponsor became aware of the reportable event or new information regarding a previously reported event.

Reporting Format from the Sponsor to the Competent Authority:

- The MDCG serious adverse event collective table will be used for regular reporting.

Annual Safety report:

- An annual safety report will be provided.
    - The annual safety report will contain a list of all SAEs that have occurred during the clinical investigation in Denmark, a benefit-risk assessment and a conclusion on the safety of the enrolled patients.

The sponsor will report any serious adverse event and the annual safety report to the functional mailbox: med-udstyr@dkma.dk

19. Informed Consent

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

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

Boston Scientific Corporation 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 center's IEC. 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 center in obtaining a written consent translation. Translated consent forms must also have IEC 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 ICF, 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 center 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. Any violations of the informed consent process must be reported as deviations to the sponsor and local regulatory authorities (e.g., IEC), 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 IEC. The new version of the ICF must be approved by the IEC. Acceptance by Boston Scientific is required if changes to the revised ICF are requested by the center's IEC. The IEC will determine the subject population to be re-consented.

20. Committees

20.1. *Safety Monitoring Process*

To promote early detection of safety issues, the Clinical Events Committee (see Section **20.1.1**) will provide evaluations of pre-specified safety events. Success of this program requires dynamic collection of unmonitored data as soon as the event is reported.

This is expedited through BSC or its designee, which is responsible for coordinating the collection of information for the subject dossier from the centers and core laboratory.

The BSC personnel from the Medical Safety and Safety Teams review safety data as they are reported by the centers throughout the duration of the study. During regularly scheduled monitoring activities, clinical research monitors further support the dynamic reporting process 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 (see Section **18**).

20.1.1. 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, including cardiovascular interventional therapy, cardiovascular surgery, and neurology, which reviews and adjudicates important endpoints and relevant adverse events reported by study investigators. The CEC will review a safety event dossier, which may include copies of subject source documents provided by study centers and adjudicate study endpoint related clinical events. The responsibilities, qualifications, membership, and committee procedures of the CEC are outlined in the CEC Charter.

The CEC will review the following events for this study.

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

21. Suspension or Termination

21.1. *Premature Termination of the Study*

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

21.1.1. 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 IEC 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 BSC to suspend or discontinue development of the device.

21.2. *Termination of Study Participation by the Investigator or Withdrawal of IEC Approval*

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

21.3. *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 centers by BSC. The IEC 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 IEC terminates participation in the study, participating investigators, associated IECs, and regulatory authorities, as applicable, will be notified in writing. Detailed information on how enrolled subjects will be managed thereafter will be provided by BSC.

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 BSC.

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

21.4. *Criteria for Suspending/Terminating a Study Center*

Boston Scientific Corporation reserves the right to stop the inclusion of subjects at a study center at any time after the study initiation visit if no subjects have been enrolled for a period

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

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

22. Study Registration and Results

22.1. *Study Registration*

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

22.2. *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, IECs, 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.

22.3. *Publication Policy*

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

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

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

23. Reimbursement and Compensation for Subjects

23.1. *Subject Reimbursement*

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

23.2. *Compensation for Subject's Health Injury*

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

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25. Abbreviations and Definitions

25.1. *Abbreviations and Acronyms*

Abbreviations and acronyms are shown in **Table 25.1-1**.

Table 25.1-1: Abbreviations and Acronyms

Abbreviation/Acronym	Definition
ADE	adverse device effect
AE	adverse event
AF	atrial fibrillation
ASD	atrial septal defect
AV	atrioventricular
BSC	Boston Scientific Corporation
CE	*Conformité Européenne*
CEC	Clinical Events 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 form
CT	computed tomography
DOAC	direct oral anticoagulant
DRT	device related thrombus
EC	exclusion criterion
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GDPR	General Data Protection Regulation
GI	gastrointestinal
HAT	hypoattenuated thickening
HAS-BLED	hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly, drugs/alcohol concomitantly
HCP	health care personnel
IC	inclusion criterion
ICE	intracardiac echocardiography
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IFU	Instructions for Use
INR	international normalized ratio
ISTH	International Society on Thrombosis and Haemostasis
ITT	intention-to-treat
LA	left atrium
LAA	left atrial appendage
LAAC	left atrial appendage closure
LAAO	left atrial appendage occlusion
MI	myocardial infarction
MRI	magnetic resonance imaging

Table 25.1-1: Abbreviations and Acronyms

Abbreviation/Acronym	Definition
mRS	Modified Rankin Scale score
NIHSS	National Institutes of Health Stroke Scale
NOAC	Non-VKA oral anticoagulant
NSTEMI	Non-ST elevation myocardial infarction
NVAF	nonvalvular atrial fibrillation
OAC	oral anticoagulant
PET	polyethylene terephthalate
PFO	patent foramen ovale
PVDF-HFP	polyvinylidene difluoride-hexafluoropropylene
RCT	randomized controlled trial
RO	radiopaque
SADE	serious adverse device effect
SAE	serious adverse event
SAPT	single antiplatelet therapy
SE	systemic embolism
SPHT	Serious Public Health Threat
STEMI	ST-elevation myocardial infarction
TEE	transesophageal Doppler echocardiography
TIA	transient ischemic attack
UADE	unanticipated adverse device effect
USADE	unanticipated serious adverse device effect
VTE	venous thromboembolic

25.2. *Definitions*

Terms are defined in **Table 25.2-1**. See **Table 25.1-1** for a list of abbreviations.

Table 25.2-1: 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.
BLEEDING [39,40,42,43]	**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

Table 25.2-1: Definitions

Term	Definition
	• 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. • Requiring nonsurgical, medical intervention by a health-care professional, AND/OR • Leading to hospitalization or increased level of care, AND/OR • Prompting evaluation Type 3 • Type 3a o Overt bleeding plus hemoglobin drop of 3 to < 5 g/dL (provided hemoglobin drop is related to bleed) o Any transfusion with overt bleeding • Type 3b o Overt bleeding plus hemoglobin drop ≥5 g/dL (provided hemoglobin drop is related to bleed) o Cardiac tamponade o Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid) o Bleeding requiring intravenous vasoactive agents • Type 3c o Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does not include intraspinal) o Subcategories confirmed by autopsy or imaging or lumbar puncture o Intraocular bleed compromising vision Type 4 • Coronary bypass graft-related bleeding

Table 25.2-1: Definitions

Term	Definition
	• 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 o Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious • Type 5b Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation
CARDIAC TAMPONADE	Evidence of a new pericardial effusion associated with hemodynamic instability and clearly related to the implant procedure. Clinical syndrome caused by the accumulation of fluid in the pericardial space, resulting in reduced ventricular filling and subsequent hemodynamic compromise.
CLINICAL EVENTS COMMITTEE (CEC) EVENT	For the WATCHMAN FLX Pro CT study, CEC events include the following: • Mortality • Stroke • Bleeding (ISTH major and non-major clinically significant) • Systemic embolism • Pericardial effusion/tamponade requiring pericardiocentesis or surgery • Other events, at the discretion of Boston Scientific
DATA CATEGORIES	Data categories as defined by GDPR are listed below. <u>Personal Data:</u> GDPR defines “Personal Data” to be any information relating to an identified or identifiable natural person (‘data subject’); an identifiable natural person is one who can be identified, directly or indirectly, in particular by reference to an identifier such as a name, an identification number, location data, an online identifier or to one or more factors specific to the physical, physiological, genetic, mental, economic, cultural or social identity of that natural person. <u>Sensitive Personal Data:</u> GDPR defines “Sensitive Personal Data” as a subset of Personal Data, which, due to their nature have been classified as deserving additional privacy and security protections because their processing may create a risk for an individual’s fundamental right and freedom. This subset includes but is not limited to the following: racial, ethnic origin or ethnicity; political opinions; religious or philosophical beliefs; trade union membership; genetic data; biometric data for the purpose of uniquely identifying a natural person; health data (including gender, family medical history, etc.); sex life or sexual orientation; criminal records or allegations of crimes (requires an even higher standard of protection). <u>Identifiers:</u> “Identifiers” are Personal Data that can be used alone or in combination with other identifiers to identify an individual. Identifiers include but are not limited to the following:

Table 25.2-1: Definitions

Term	Definition
	• All government-issued identification numbers (including but not limited to names, social security number, certificate/license numbers, passport, national ID) • All financial account numbers (including but not limited to bank account numbers, payment numbers, bank or credit card numbers) • All geographic subdivisions smaller than a state, including street address, city, county, precinct, ZIP code, and their equivalent geocodes, except for the initial three digits of the ZIP code if, according to the current publicly available data from the Bureau of the Census, the geographic unit formed by combining all ZIP codes with the same three initial digits contains more than 20,000 people and/or the initial three digits of a ZIP code for all such geographic units containing 20,000 or fewer people is changed to 000 • All elements of dates (except year) for dates that are directly related to an individual, including birth date, admission date, discharge date, death date, and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older • Telephone numbers • Fax numbers • Device identifiers and serial numbers • E-mail addresses • Web Universal Resource Locators (URLs) • Internet Protocol (IP) addresses • Medical record numbers • Biometric identifiers, including finger and voice prints • Health plan beneficiary numbers • Full-face photographs and any comparable images Any other unique identifying number, characteristic, or code (including subject ID number)
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 implant procedure, any procedure-related death within 30 days after the implant procedure or during postoperative hospitalization for the implant 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)

Table 25.2-1: Definitions

Term	Definition
	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 Pro device without in-hospital mortality
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.
GENERAL DATA PROTECTION REGULATION	The General Data Protection Regulation (GDPR) is a legal framework that sets guidelines for the collection and processing of personal information of individuals within the European Union.
MAJOR ENDOVASCULAR INTERVENTION	Examples include events such as pseudoaneurysm repair, AV fistula repair, or other major endovascular repair. **Note 1:** Percutaneous catheter drainage of pericardial effusions, snaring of an embolized device, thrombin injection to treat femoral pseudoaneurysm and nonsurgical treatments of access site complications are NOT considered major endovascular repairs.
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.

Table 25.2-1: Definitions

Term	Definition
NON-VALVULAR ATRIAL FIBRILLATION	Atrial fibrillation in the absence of moderate-to-severe mitral stenosis or in the absence of a mechanical heart valve.

PERICARDIAL EFFUSION[44]	Severity of pericardial effusion, with or without cardiac tamponade, is defined by the clinical therapy associated with the effusion.
	• Clinically non-relevant
	  o Requiring no intervention
	  o Treated pharmacologically
	• Clinically relevant
	  o Treated with therapeutic pericardiocentesis
	  o Treated with surgical intervention
	  o Requiring blood transfusion
	  o Resulting in shock and/or death

PROCEDURE-RELATED EVENTS	Events occurring during or as a direct result of the implant 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.
SERIOUS PUBLIC HEALTH THREAT (per EU MDR 2017/745)	An event which could result in imminent risk of death, serious deterioration in a person's state of health, or serious illness, that may require prompt remedial action, and that may cause significant morbidity or mortality in humans, or that is unusual or unexpected for the given place and time.
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[45,46]	**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

Table 25.2-1: Definitions

Term	Definition
	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 vascular insufficiency or occlusion of the extremities or any non-CNS organ associated with clinical, imaging, surgical/autopsy evidence of arterial

Table 25.2-1: Definitions

Term	Definition
	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.

Abbreviations: ADE=adverse device effect; AE=adverse event; CEC=Clinical Events Committee; CNS=central nervous system; CT=computed tomography; GDPR=General Data Protection Regulation; ISTH=International Society on Thrombosis and Haemostasis; LAA=left atrial appendage; MRI=magnetic resonance imaging; mRS=Modified Rankin Scale score; SADE=serious adverse device effect; SAE=serious adverse event; TIA=transient ischemic attack; USADE=unanticipated serious adverse device effect