Hong Kong WATCHMAN FLX™ Observation

HK FLX

Study Reference：S2461

CLINICAL INVESTIGATION PLAN

Sponsored By

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Original Release: September 2，2019

Current Version: D

Revision Version	Protocol Date	Template number and version	Protocol Section Modified	Summary of Changes	Justification for Modification
AA	**September 2, 2019**	**92120219 _Rev / Ver. C**	**N/A**	**N/A**	**Initial Release**
B	**September18，2019**	**92120219 _Rev / Ver. C**	**Headers**	**Updated the study name and all have the same Rev/Ver number**	**Consistent the study name with CTMS**
B	**September18，2019**	**92120219 _Rev / Ver. C**	**Contact Information**	**Updated Coordinating Principal Investigators information**	**Typo**
C	**November29，2019**	**92120219 _Rev / Ver. C**	**Contact Information**	**Updated Coordinating Principal**	**Principal Investigators Changed**

Revision Version	Protocol Date	Template number and version	Protocol Section Modified	Summary of Changes	Justification for Modification
				Investigators information	
D	**July 19, 2021**	**92120219 _Rev / Ver. G**	**Contact Information**	**Updated clinical contact information**	**Clinical contact changed**
D	**July 19, 2021**	**92120219 _Rev / Ver. G**	**8.1 Scale and Duration**	**Deleted the below limitations on the number of subjects enrolled per site:** **"Each site might enroll a maximum of 25 subjects."**	**Given the influence of COVID-19 on the progress of subject enrollment, delete the limitations on the enrollment ceiling for each site. It is estimated this change will not significantly affect the study results.**
D	**July 19, 2021**	**92120219 _Rev / Ver. G**	**Table of Contents;** **11.1 Data Collection;** **20. Safety Reporting**	**Updated the page number in table of content, and the table number**	**Updated due to protocol mofification**
D	**July 19, 2021**	**92120219 _Rev / Ver. G**	**Header**	**Updated version number from "Ver C" to "Ver D"**	**Protocol updated**

2. Protocol Synopsis

Hong Kong WATCHMAN FLX™ Observation HK FLX	
Study Objective(s)	The primary objective of this study is to observe the safety and effectiveness of the WATCHMAN FLX™ Left Atrial Appendage Closure (LAAC) Device for subjects with non-valvular atrial fibrillation to reduce the risk of stroke in Hong Kong area.
Device	The WATCHMAN FLX Left Atrial Appendage Closure Device with Delivery System (consisting of the Delivery Catheter with a pre-loaded Closure Device)
Device Sizes	WATCHMAN FLX is available in 20, 24, 27, 31, and 35mm models to fit left atrial appendage ostia widths ranging from 14.0 – 31.5mm.
Study Design	This study is a prospective, non-randomized, multi-center observational study.
Planned Number of Subjects	Up to 50 subjects will be enrolled in the study. Each investigational site might have up to 2 roll-in subjects, which is included in the 50 total subjects.
Planned Number of Sites	Up to 5 investigational centers in Hong Kong.
Primary Effectiveness Endpoint	The occurrence of non-effective LAA closure defined as any peri-device flow > 5mm demonstrated by TEE/CT/MRI at First Follow-up.
Primary Safety Endpoint	The occurrence of one of the following events between the time of implant and within 7 days following the procedure or by hospital discharge, whichever is later: all-cause death, ischemic stroke, systemic embolism, or device- or procedure-related events requiring open cardiac surgery or major endovascular intervention such as pseudoaneurysm repair, AV fistula repair, or other major endovascular repair. Percutaneous catheter drainage of pericardial effusions, snaring of an embolized device, thrombin injection to treat femoral pseudoaneurysm and nonsurgical treatments of access site complications are excluded from this endpoint.

Hong Kong WATCHMAN FLX™ Observation HK FLX	
Secondary Endpoint	The occurrence of ischemic stroke or systemic embolism at 12 months from the time of implant.
Additional Analysis	The occurrence of stroke (including ischemic and/or hemorrhagic), cardiovascular death (cardiovascular and/or unexplained cause) and systemic embolism.
Follow-up Schedule	Study procedures and follow-up visits will occur as follows: • Enrollment Visit • WATCHMAN FLX Implant • First Follow-up (30-100 days) • 12-Month Follow-up (365 ±30 days)
Study Duration	Enrollment is expected to be completed in approximately 12 months and each subject is expected to be followed for approximately 12 months with primary endpoints collected at First Follow-up (30-100 days); therefore the total study duration is estimated to be approximately 24 months.
Participant Duration	The study duration for each subject is expected to be approximately 12 months.
Inclusion Criteria	1. Patients who are eligible for a WATCHMAN FLX device according to current international and local guidelines (and future revisions) and per physician discretion; 2. Patients who are willing and capable of providing informed consent, participating in all testing associated with this clinical investigation at an approved clinical investigational center; 3. Patients whose age is 18 years or above, or of legal age to give informed consent specific to state and national law.
Exclusion Criteria	1. Patients who are currently enrolled in another investigational study or registry that would directly interfere with the current study, except when the patient is participating in a mandatory governmental registry, or a purely observational registry with no associated treatments. Each instance should be brought to the attention of the sponsor to determine eligibility.

<table>
<tr><th colspan="2">Hong Kong WATCHMAN FLX™ Observation
HK FLX</th></tr>
<tr><td></td><td>2. Women of childbearing potential who are, or plan to become, pregnant during the time of the study (method of assessment upon physician's discretion);
3. The subject is unable or not willing to complete follow-up visits and examination for the duration of the study.</td></tr>
<tr><td>Multiple Interventions During Treatment/Implant</td><td>Multiple interventions are allowed in the study.</td></tr>
<tr><td colspan="2">Statistical Methods</td></tr>
<tr><td>Primary Statistical Hypothesis</td><td>There is no hypotheses testing in this small sample size observational study.</td></tr>
<tr><td>Statistical Test Method</td><td>Descriptive statistics will be conducted for the endpoint events.
For the Primary Effectiveness Endpoint, it might be considered reasonable if up to 3 primary effectiveness endpoint events should occur in this small sample size study.
For the Primary Safety Endpoint, it might be considered reasonable if up to 3 primary safety endpoint events should occur in this small sample size study.</td></tr>
<tr><td>Sample Size Parameters</td><td>No formal sample size calculation is performed because there is no formal hypothesis testing in the study. The following table provides a 95% confidence interval (exact methods) for a sample size of 50 if there are 0 ~ 5 events.
<table>
<tr><th>Events</th><th>Rates (n=50)</th><th>Lower 95%CI</th><th>Upper 95%CI</th></tr>
<tr><td>0</td><td>0%</td><td>0.0%</td><td>7.1%</td></tr>
<tr><td>1</td><td>2%</td><td>0.1%</td><td>10.6%</td></tr>
<tr><td>2</td><td>4%</td><td>0.5%</td><td>13.7%</td></tr>
<tr><td>3</td><td>6%</td><td>1.3%</td><td>16.5%</td></tr>
<tr><td>4</td><td>8%</td><td>2.2%</td><td>19.2%</td></tr>
<tr><td>5</td><td>10%</td><td>3.3%</td><td>21.8%</td></tr>
</table></td></tr>
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3.1. *Table of Figures*

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4. Introduction

4.1. *Background*

Atrial fibrillation (AF) is one of the most common abnormal rhythm disturbances and affects approximately 5.5 million people worldwide, including 10% of people older than 75 [1]years. The most debilitating consequence of AF is thrombus formation from stagnant blood flow leading to thromboembolism and stroke. As such, the rate of ischemic stroke attributed to non-valvular AF is estimated to average 5% per year, which is 2-7 times that of those without AF[2].

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

Currently available alternatives to warfarin are the direct oral anticoagulants (DOACs), which include dabigatran, rivaroxaban, apixaban, and edoxaban. Unlike warfarin, DOACs can be administered without the need for monitoring, have fewer food and drug interactions, and provide an improved effectiveness/safety ratio. Dabigatran at the dose of 150 mg twice daily is shown to be superior to warfarin in prevention of stroke and systemic thromboembolism, has a favorable safety profile including significantly less intracranial bleeding and comparable extracranial bleeding, and is associated with less cardiovascular mortality [6-9]. Rivaroxaban at a daily dose of 20 mg is shown to be noninferior to warfarin in prevention of stroke or systemic embolism. The risk of major bleeding is not significantly different for rivaroxaban versus warfarin; however, intracranial and fatal bleeding is less frequent with rivaroxaban [10]. In comparison to warfarin, apixaban at a dose of 5 mg twice daily is also shown to be superior in prevention of stroke and systemic thromboembolism, causes less bleeding, and is associated with a lower mortality rate [11]. Edoxaban is shown to be non-inferior to warfarin with respect to the prevention of stroke or systemic embolism, and is associated with significantly lower rates of bleeding and death from cardiovascular causes [12]. While DOACs eliminate the need for frequent monitoring, dosage adjustments, and dietary and metabolic interactions, there are still concerns of patient compliance and bleeding complications with these newer agents.

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

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

4.2. *WATCHMAN Therapy*

Two generations of the WATCHMAN Closure Device with Delivery System, as identified in the Table 1, are discussed below. The WATCHMAN Access System, required accessory for use in WATCHMAN procedures, and each generation of the WATCHMAN Closure Device with Delivery System are provided sterile and as single use devices.

Table 1: Description of WATCHMAN Products

Name	Description
WATCHMAN™ Access System	The first CE-marked and FDA-approved generation of the WATCHMAN Access System. This Access System may be used with either the WATCHMAN (Gen 2.5) or WATCHMAN FLX Closure Device with Delivery System
WATCHMAN™ LAA Closure Device with Delivery System	The first commercialized generation of the WATCHMAN LAA Closure Device with Delivery System (note: also referred to internally as Gen 2.5).
WATCHMAN FLX™ Closure Device with Delivery System	Boston Scientific's next generation WATCHMAN LAA Closure Device with Delivery System.

For simplicity, the two generations of the Closure Device with Delivery System will be referenced as WATCHMAN (Gen 2.5) and WATCHMAN FLX and the implanted portion of the products will be referred to as the Closure Device.

The implanted component of the study device, hereafter referred to as the WATCHMAN FLX Device, is designed to prevent the embolization of thrombi that may form in the LAA. The WATCHMAN FLX Device may reduce the occurrence of ischemic stroke and systemic thromboembolism in patients with non-valvular AF who require treatment for potential thrombus formation. It may also reduce the risk of life-threatening bleeding events such as hemorrhagic stroke by potentially removing the need for anticoagulation therapy.

Various clinical trials have established the safety and performance of the WATCHMAN LAA Closure Technology (Access System and Delivery System) which is designed to prevent thrombus embolization from the left atrial appendage and reduce the risk of life-threatening bleeding events in patients with non-valvular atrial fibrillation. Table 2 outlines the various clinical trials. All devices tested in these trials utilized the WATCHMAN (Gen 2.5) Closure Device except for EVOLVE. The EVOLVE study tested safety and efficacy in what was at the time the next-generation WATCHMAN (Gen 4) device.

Table 2: Clinical Studies of the WATCHMAN™ Device

Study	Dates of Enrollment	Enrolled Subjects	Sites	Follow-Up

Pilot (feasibility study)	Aug 2002 – Jan 2005	66	8	U.S. subjects completed 5 years; OUS subjects completed up to 9 years.
PROTECT AF (pivotal study)	Feb 2005 – Jun 2008	800	59	Complete through 5 years
CAP Registry	Aug 2008 – Jun 2010	566	26	Complete
ASAP (feasibility study)	Jan 2009 – Nov 2011	150	4	Complete
EVOLVE (registry)	May 2009 – June 2011	69	3	Complete
PREVAIL (pivotal study)	Nov 2010 – Jun 2012	461	41	Complete
CAP2 Registry	Sep 2012 – Mar 2014	579	47	Ongoing through 5 years
EWOLUTION (EU registry)	Oct 2013 – May 2015	1025	47	Ongoing through 2 years
WASP (Asia Pacific Registry)	Jan 2014 – Oct 2015	201	9	Ongoing through 2 years
WATCHMAN NESTed (US PAS)	Dec 2016-present	2000	All commercial sites	Ongoing through 5-years
SALUTE (Japan study)	Feb 2017-July 2017	71	10	Ongoing through 2 years
ASAP-TOO (OAC contraindicated population)	Feb 2017-present	888	Up to 100	Ongoing through 5-years

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

The first pivotal study, WATCHMAN Left Atrial Appendage System for Embolic PROTECTion in Patients with Atrial Fibrillation[13] (PROTECT- AF), demonstrated non-inferiority of the WATCHMAN Device to long-term warfarin therapy for the primary effectiveness endpoint of stroke, systemic embolism, and cardiovascular death.

The most recent, published analysis of the PROTECT AF[14] trial has shown that the WATCHMAN Device achieved superiority for the combined endpoint of all stroke, cardiovascular or unexplained death and systemic embolism (for Bayesian analysis, posterior probabilities are used to determine superiority; > 95% represents superiority).

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

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

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

- Cardiovascular Mortality: the WATCHMAN group was superior to the control group, 1.0 percent% and 2.4 percent % respectively, representing a 60 percent% relative risk reduction in cardiovascular death in the WATCHMAN group (HR = 0.40, p=0.0045).

The Continued Access to PROTECT Registry[15] (CAP Registry) provided continued access of the WATCHMAN Device to PROTECT- AF investigators and demonstrated a decrease in procedural complications of pericardial effusion with tamponade, cardiac perforation, and device embolization (1.2%, 0.2%, 0%, respectively).

The second pivotal study, Prospective Randomized Evaluation of the WATCHMAN LAA Closure Device In Patients with Atrial Fibrillation Versus Long Term Warfarin Therapy (PREVAIL), was conducted to provide additional information on the implant procedure and complication rates associated with the device. [16] In this trial, LAA occlusion was non-inferior to warfarin for ischemic stroke prevention or systemic embolism (SE) >7 days' post-procedure. Although non-inferiority was not achieved for overall efficacy, event rates were low and numerically comparable in both arms. Procedural safety has significantly improved over the previous trials, PROTECT AF and CAP. PREVAIL only data, data from subjects enrolled in the PREVAIL study without the prior PROTECT AF study information used in the Bayesian analysis, showed that the ischemic stroke rate (2.3 vs. 0.3 per 100 pt-years) favored to the Control group, while the hemorrhagic stroke rate (0.4 vs. 0.7 per 100 pt-years) and death (cardiovascular or unexplained) rate (1.4 vs. 2.3 per 100 pt-years) favored the WATCHMAN group. The PREVAIL trial provides additional data that LAA occlusion is a reasonable alternative to warfarin therapy for stroke prevention in patients with NVAF who do not have an absolute contraindication to short-term warfarin therapy.

The Continued Access Protocol (CAP2) was a prospective, non-randomized, multicenter study to allow continued access to the WATCHMAN LAA Closure Technology during the data analysis, reporting and review of the PREVAIL pivotal study Pre-Market Application by FDA. The first of 578 subjects was enrolled on 25-Sep-2012. The final subjects were enrolled on 21-Mar-2014, and are currently in long-term follow-up out to 5 years. Subjects in this trial were at a high-risk of stroke with a mean CHA_2DS_2-VASc of 4.5 (+/- 1.3). Additionally, 98% were at moderate to high risk of bleeding. Patients in this trial had an ischemic stroke rate of 2.3%, which is in line with the other WATCHMAN trials.

The purpose of the EValuation of the Next Generation WATCHMAN LAA Closure TechnOLogy in Non-Valvular AF PatiEnts (EVOLVE) study was to evaluate the implantability of the Gen 4 WATCHMAN LAA Closure Device in patients with non-valvular

atrial fibrillation (AF) with a $CHADS_2$ stroke risk stratification of 1 or greater. The primary objectives of the study were to assess successful delivery and release of the WATCHMAN (Gen 4) Closure Device, the occurrence of serious pericardial effusions and the discontinuation of warfarin at 45 days. Patients who had non-valvular paroxysmal, persistent or permanent AF, had a $CHADS_2$ score of ≥1, and were eligible for warfarin therapy were screened as candidates for the study and implant.

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

The REgistry on WATCHMAN Outcomes in Real-Life Utilization (EWOLUTION) study is an observational, prospective, single-arm, multicenter clinical study (Europe, Middle East, Russia) that compiles real-world clinical outcome data for WATCHMAN LAA Closure Device in a commercial setting and collects health care usage data for reimbursement decisions in certain countries; EWOLUTION continues to build on the existing WATCHMAN clinical database. EWOLUTION is a purely observational post-market data collection study. Consecutive enrollment was strongly encouraged, and achieved in most sites, to minimize selection bias and maintain the strengths of a large-scale, all-comers clinical registry. A total of 1025 patients scheduled for a WATCHMAN implant at 47 centers in 13 countries were enrolled, and subjects are being followed for two years after WATCHMAN implantation according to standard medical practice. Analyses include procedural and long-term data, including stroke/embolism, bleeding, and death.

Preliminary baseline/implant data, the results of the peri-procedural analyses, and data through the 3-month visit were presented for 1020 subjects. The EWOLUTION population was at high risk for stroke presenting with $CHADS_2$ (2.8±1.3) and CHA_2DS_2-VASc (4.5±1.6) scores. The populations had a moderate-to-high risk of bleeding with an average HAS-BLED score: 2.3 ±1.2. Approximately 72% of patients in EWOLUTION were deemed unsuitable for OAC by their physician. The device was successfully deployed in 98.5% of patients with no or minimal residual flow achieved in 99.7% of implanted patients. There were twenty-six (2.8%, 1.6–3.6%) serious adverse events occurring in 23 subjects reported as relating to the procedure at 7 days. Three patients died within 30 days of causes that appear unrelated to the device. These rates of procedural success and 7-day device-related SAEs were lower than those found in PROTECT AF, CAP, PREVAIL, and CAP2.

The WATCHMAN ASia Pacific Registry (WASP) is an Asia/Pacific registry with identical design to EWOLUTION that compiles real-world clinical outcome data for the

WATCHMAN LAA Closure Device in a commercial setting and collects health care usage data for reimbursement decisions in certain countries. Like EWOLUTION, WASP is a purely observational post-market data collection study.

The ASA Plavix Study with WATCHMAN Left Atrial Appendage Closure Technology (ASAP) study was a multi-center, prospective non-randomized study of 150 subjects enrolled at four sites in Europe. Subjects were followed post-implant at 3, 6, 12, 18, and 24 months. The primary objective of this study was to characterize the performance of the WATCHMAN Left Atrial Appendage (LAA) Closure Device in non-valvular atrial fibrillation subjects for which warfarin therapy was contraindicated. The study demonstrated a high procedure success with the WATCHMAN device placed in 94.0% of all procedures attempted. All cause death was the most prevalent adverse event, occurring in fourteen (14) subjects. The next most frequent event was device thrombus (8). Of the cases of device thrombus one (1) was associated with an ischemic stroke event. The remaining seven (7) events of device thrombus were treated with low molecular weight heparin until resolution. Ischemic stroke was reported in four (4) subjects for a rate of 1.5 per 100 pt-yrs. This rate is significantly lower than other trials assessing stroke rates in subjects with atrial fibrillation who are unable to take anticoagulant therapy

SALUTE is a study to evaluate the SAfety and effectiveness of the Left atrial appendage closure therapy for patients with non-valvUlar atrial fibrillation at increased risk of ThromboEmbolism in Japanese medical environment. Enrollment is complete and the trial is in long-term follow-up.

The Assessment of the WATCHMAN™ Device in Patients Unsuitable for Oral Anticoagulation (ASAP-TOO) Study is designed to establish the safety and effectiveness of the WATCHMAN™ Left Atrial Appendage Closure Device, including the post-implant medication regimen, for subjects with non-valvular atrial fibrillation who are deemed not to be eligible for anticoagulation therapy to reduce the risk of stroke. The device is intended to reduce the risk of thromboembolic ischemic stroke and systemic embolism. This trial began enrollment in February of 2017 and will randomize 888 subjects at up to 100 worldwide centers.

The first iteration of the WATCHMAN FLX Device began a limited market release (LMR) in Europe in 2015 and was implanted in 213 patients. The rate of embolization (3.8%) for this initial FLX iteration was greater than anticipated. Boston Scientific elected to make design enhancements to the device. These design enhancements were incorporated into the current WATCHMAN FLX Device. The PINNACLE FLX study is designed to establish the safety and effectiveness of the WATCHMAN FLX™ Left Atrial Appendage Closure (LAAC) Device for subjects with non-valvular atrial fibrillation. The study completed the enrollment of 398 subjects on November 9, 2018. Each subject will be followed for 2 years. However, the PINNACLE FLX study is conducted exclusively in the U.S. Although it is assumed that ethnic difference might not play an important role in the performance of the left atrial appendage closure, we designed this HK FLX study to observe the safety and effectiveness of the WATCHMAN FLX™ LAAC Device for subjects with non-valvular atrial fibrillation to reduce the risk of stroke in Hong Kong area.

5. Device Description

5.1. *Product Description*

The WATCHMAN FLX Delivery System consists of the Delivery Catheter and the pre-loaded Closure Device, **Figure 1**. The WATCHMAN FLX Delivery System is used in conjunction with a WATCHMAN Access System. Together, the WATCHMAN Access System and WATCHMAN FLX Delivery System permit device placement in the LAA via femoral venous access and crossing the inter-atrial septum into the left atrium. The WATCHMAN Access System is commercially-available and a required accessory for use with the WATCHMAN FLX procedures.

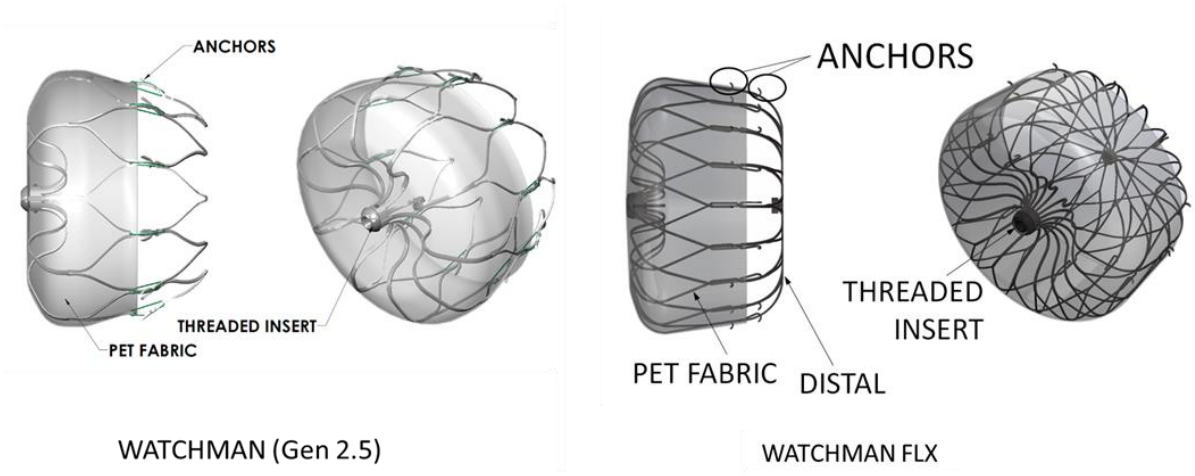
5.1.1. WATCHMAN FLX Delivery System and with Pre-loaded LAAC Device

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

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

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

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



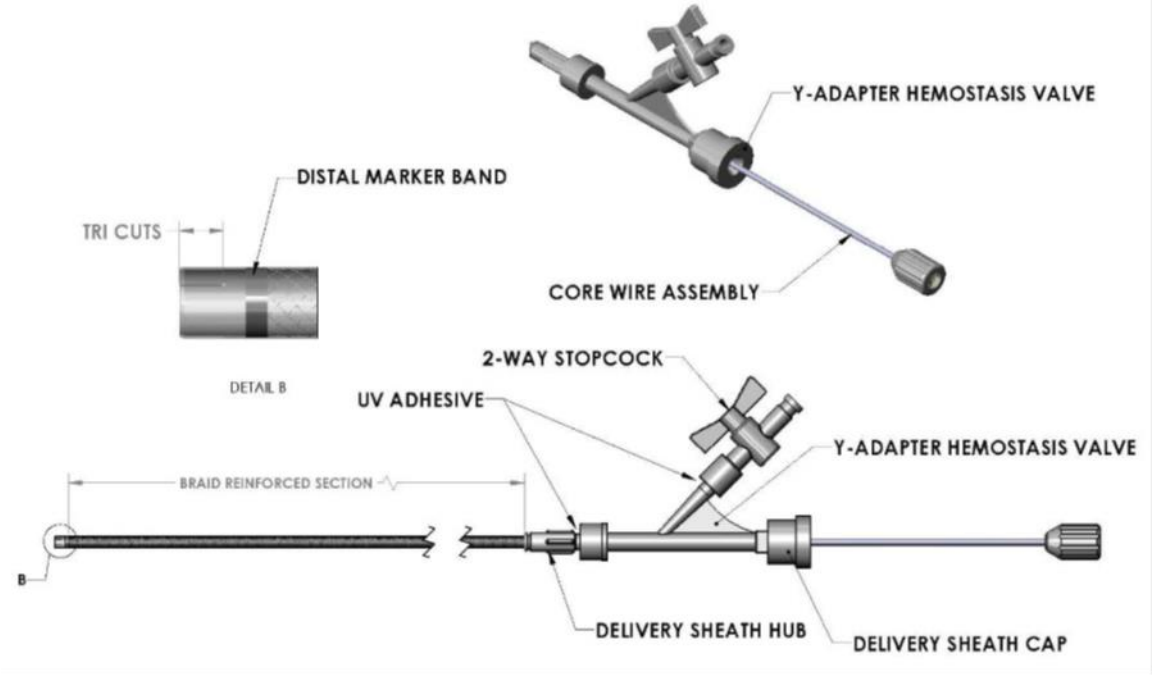
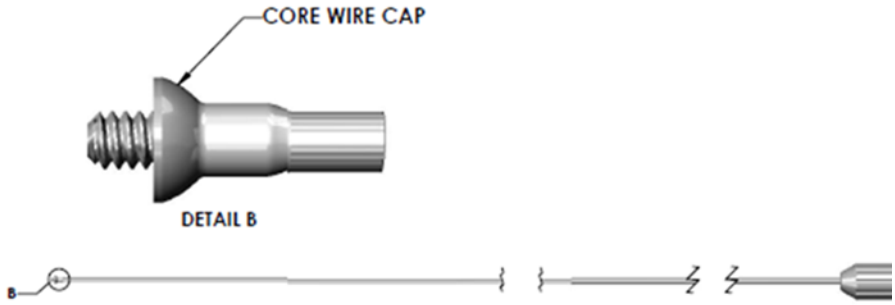


Illustration of WATCHMAN FLX Delivery Sheath Assembly



- Illustration of WATCHMAN FLX Core Wire

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

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

- Closed Distal End – Provides improved deployment stability and control, with atraumatic distal structure.

- Fully Recapturable and Redeployable – Decreases the number of devices used and sheath exchanges per case, which may reduce procedure time and complications associated with sheath exchange.
- Decreased Recapture Force – Improves user experience.
- Increased Conformability – Creates better left atrial appendage seal due to the increased number of contact points around the LAA ostium, designed to promote short-term healing.
- Decreased Exposed Metal Volume on Proximal Face – May promote short-term healing.
- Enhanced Radiopacity – Improves visibility under fluoroscopy.
- Shorter Device Length – Allows for treatment of shorter appendages.
- Greater Device Use Range – Provides for treatment of a wider range of appendage sizes.

6. Study Objectives

The primary objective of this study is to observe the safety and effectiveness of the WATCHMAN FLX™ Left Atrial Appendage Closure (LAAC) Device for subjects with non-valvular atrial fibrillation to reduce the risk of stroke in Hong Kong area.

Compared with PINNACLE FLX study conducted in the U.S., the data collected in this study maybe used for product registration in other areas to show that ethnic difference might not play an important role in the performance of WATCHMAN FLX™.

7. Study Endpoints

7.1. *Primary Effectiveness Endpoint*

The occurrence of non-effective LAA closure defined as any peri-device flow > 5mm demonstrated by TEE/CT/MRI at First Follow-up.

7.2. *Primary Safety Endpoint*

The occurrence of one of the following events between the time of implant and within 7 days following the procedure or by hospital discharge, whichever is later: all-cause death, ischemic stroke, systemic embolism, or device or procedure related events requiring open cardiac surgery or major endovascular intervention such as pseudoaneurysm repair, AV fistula repair, or other major endovascular repair.

NOTE: Percutaneous catheter drainage of pericardial effusions, snaring of an embolized device, thrombin injection to treat femoral pseudoaneurysm and nonsurgical treatments of access site complications will be captured as adverse events (AEs), and are excluded from this endpoint.

7.3. *Secondary Effectiveness Endpoint*

The occurrence of ischemic stroke or systemic embolism at 12 months from the time of implant.

7.4. *Additional analysis*

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

8. Study Design

This study is a prospective, non-randomized, multi-center observational study.

8.1. *Scale and Duration*

Up to 50 subjects at up to 5 investigational centers in Hong Kong will be enrolled in the study. Each investigational site might have up to 2 roll-in subjects, which is included in the 50 total subjects.

Enrollment is expected to be completed in approximately 12 months and each subject is expected to be followed for approximately 12 months with primary endpoints collected at First Follow-up (30 ~ 100 days); therefore the total study duration is estimated to be approximately 24 months.

The study duration for each subject is expected to be approximately 12 months.

8.2. *Justification for the Study Design*

WATCHMAN FLX is new generation of the WATCHMAN product, and its safety and effectiveness in being verified in the PINNACLE FLX study conducted in the U.S. Although it is assumed that ethnic difference might not play an important role in the performance of the left atrial appendage closure, this HK FLX study is designed to observe the safety and effectiveness of the WATCHMAN FLX in Hong Kong area.

This is an observational data collection designed to compile real-world data for WATCHMAN FLX in Hong Kong. The implant of the device is decided according to the patient clinical indications, regardless of participation in the study. The post-implant TEE (or alternative imaging methods) is also a clinical standard after the procedure to ensure sealing and exclude thrombus on the device prior to stop dual platelet inhibition or warfarin. The patients are followed per standard of care including the 12-Month Follow-up, which is mainly to collect adverse events, so no additional examination or procedure is required by the study other than standard clinical practice.

9. Subject Selection

9.1. *Study Population and Eligibility*

Any patient, who meets all the inclusion criteria, does not meet any of the exclusion criteria, and who provides written informed consent may be enrolled in the study. The subjects selected for participation will be from the investigator's general patient population. The investigator has the responsibility for screening all potential patients and selecting those who meet study inclusion/exclusion criteria as described in sections 错误!未找到引用源。 and 0.

9.2. *Inclusion Criteria*

A subject may be enrolled in the study if all of the following inclusion criteria are met, provided no exclusion criteria (see section 9.3) are met:

1. Patients who are eligible for a WATCHMAN FLX device according to current international and local guidelines (and future revisions) and per physician discretion;
2. Patients who are willing and capable of providing informed consent, participating in all testing associated with this clinical investigation at an approved clinical investigational center;
3. Patients whose age is 18 years or above, or of legal age to give informed consent specific to state and national law.

9.3. *Exclusion Criteria*

Subjects will be excluded from the study if they meet any of the following criteria:

1. Patients who are currently enrolled in another investigational study or registry that would directly interfere with the current study, except when the patient is participating in a mandatory governmental registry, or a purely observational registry with no associated treatments. Each instance should be brought to the attention of the sponsor to determine eligibility.
2. Women of childbearing potential who are, or plan to become, pregnant during the time of the study (method of assessment upon physician's discretion);
3. The subject is unable or not willing to complete follow-up visits and examination for the duration of the study.

10. Subject Accountability

10.1. *Enrollment*

Subjects who meet the eligibility criteria as per 错误!未找到引用源。 and 0, have signed and dated the Informed Consent Form and actually undergo a WATCHMAN FLX implant procedure are considered enrolled in the study. Baseline data from subjects who meet the eligibility criteria as per 错误!未找到引用源。 and 0, have signed and dated the Informed Consent Form but do not eventually undergo a WATCHMAN FLX implant procedure are

collected for epidemiological reasons, to better characterize the population. The start of the WATCHMAN FLX implant procedure is considered the insertion of the WATCHMAN FLX Access Sheath.

10.2. *Withdrawal*

Every effort should be made to retain subject enrollment for the duration of the study. During the informed consent process subjects should be fully informed of the data collection requirements and duration, and should only be enrolled if willing to fully participate in it. All subjects enrolled in the clinical study must be accounted for and documented. Reasons for withdrawal may include physician discretion, subject choice to retire consent, loss to follow-up, or death. In the event a subject does decide to withdraw from the study, every effort should be made to obtain full information on any on-going adverse events.
Subjects should only be considered lost to follow-up after significant effort has been made to contact the subject. At a minimum there should be 3 documented telephone contact attempts and one certified letter sent to the subject's last known residence. Subject withdrawal and lost to follow-up will be documented on the "End of Study" CRF. For subjects who are "lost-to-follow-up" the investigator/center should make documented attempts to contact the subject prior to completion of the applicable CRF. Additional data may no longer be collected after the point at which a subject has been withdrawn from the study or withdraws his/her consent, for whatever reason. All open adverse events should be closed or documented as chronic. Data collected up to the point of subject withdrawal may be used, unless any local regulations apply which require removal of the data.

10.3. *Subject Status and Classification*

Consent Ineligible

A subject who has signed informed consent but is found to not meet eligibility criteria will be classified as "**Consent Ineligible**". There are no FU or adverse event reporting requirements for consent ineligible subjects. Subjects determined to be Consent Ineligible according to statements above do not count towards the enrollment ceiling and will not be used for analysis of the endpoints. The original signed Informed Consent must be maintained in the center's administrative file.

Intent

A subject who signs informed consent, meets eligibility criteria, but then does not undergo an implant of a WATCHMAN FLX device will be classified as "**Intent**". This definition includes subjects that do not meet echocardiographic criteria for a WATCHMAN FLX implant at the implant TEE/CT/MRI evaluation (e.g. a thrombus has developed in the LAA, inappropriate LAA size). These patients may be withdrawn immediately, unless re-assessment of the criteria is planned. If subjects are re-assessed for WATCHMAN FLX implant, as per physicians' discretion, then a reconsent must be obtained for participating in the registry.
Subjects who have been consented, but not yet implanted at the time of enrollment closure will also be classified as **Intent.** There are no FU or adverse event reporting requirements for Intent subjects. Intent subjects do not count towards the enrollment ceiling and will not be used for analysis of the endpoints. The original signed Informed Consent must be maintained in the

center's patient file. For these subjects, the eCRFs in the "Baseline" folder and a "Patient Status" form must be completed. Subjects who become Intents due to death before the implant procedure must have the death documented.

Attempt
A subject who signs informed consent, meets eligibility criteria and has had the WATCHMAN FLX Access Sheath inserted to implant the device, but eventually does not receive a WATCHMAN FLX device will be classified as "**Attempt**". These subjects may be withdrawn, unless a re-implant of a study device is planned, per physician discretion. If subjects are re-assessed for WATCHMAN FLX implant, as per physicians' discretion, then a reconsent must be obtained for participating in the registry. These subjects will be handled as "Implant" (see next section), if the re-implant is successful. Subjects who eventually have not received a WATCHMAN FLX device at the time of enrollment closure will remain classified as "Attempt" and be withdrawn. There are no FU requirements for Attempt subjects; however, adverse events will be collected up to the point of subject withdrawal. Attempt subjects count towards the enrollment ceiling and will be used for analyses of the endpoints. The original signed Informed Consent must be maintained in the center's study file and the following forms must be completed:

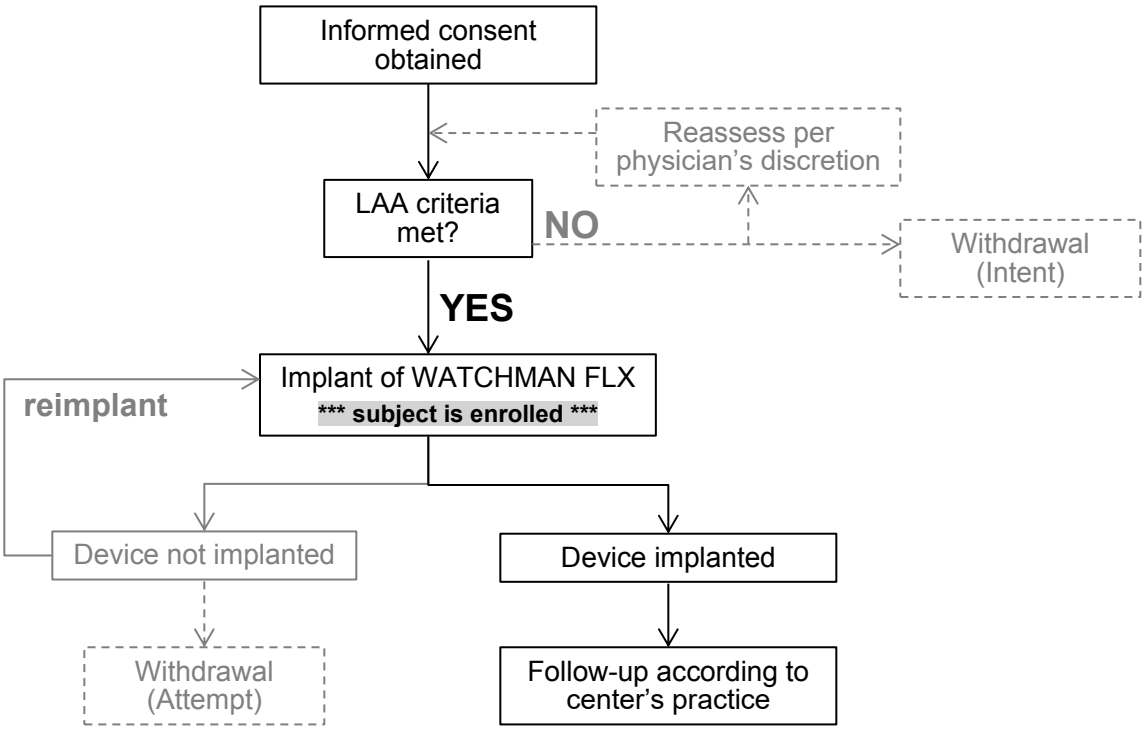
- eCRFs in the "Baseline" and "Implant" folders
- "Adverse Event" forms for any adverse event that occurs after signing the Informed Consent, up to the point of subject withdrawal.
- "Patient Status" form for withdrawal, when applicable.

The date at which the patient status form has been completed will be the point of subject withdrawal.

Implant
A subject who is successfully implanted with the WATCHMAN FLX device will be classified as "**Implant**". These subjects are followed in accordance with the FU schedule and included in all study analyses. All applicable case report forms per the protocol must be completed. The original signed Informed Consent and any relevant documentation must be maintained in the center's patient file.

Roll-in and non-roll-in
Each site might have up to 2 roll-in subjects if the site has never implanted a WATCHMAN FLX before. Roll-in subjects should be decided before the implant procedure, and might be classified as **Attempt** or **Implant** after the procedure. Roll-in subjects are enrolled and counted to the ceiling of the sample size. Other enrolled subjects are defined as non-roll-in.

Figure 2: Subject Status and Data Collection Flow Chart



11. Study Methods

11.1. *Data Collection*

To ensure data quality and completeness, all required data will be recorded on case report forms (CRFs) provided by the sponsor. Data will be entered onto electronic case report forms by the investigational site or designee. Case Report Forms should be completed accurately during and in a timely manner after any visit in the study. The Principal Investigator or appointed designee must review the case report forms and sign them, certifying their accuracy. Completed case report forms should be submitted to the sponsor within two weeks of completion of a study visit.

Each patient will be followed for a period of 12 months after implant according to the schedule and standard practice at the enrolling centers. There will be no additional procedures, for subjects who participate in the study. Subjects are expected to be followed at implant, then at First Follow-up (30 ~ 100 days), and 12-Month Follow-up (365 ±30 days) post-implant. An intermediate visit may be scheduled in a number of patients, per physician discretion.

For subjects who are not scheduled to visit the clinic for a follow-up, a subject contact (e.g. phone call) will ensure capture of the endpoint related information, however it is strongly recommended to perform an in-office visit for at least the First Follow-up visit.

Table 3 provides an overview of the data to be collected at each visit.

Table 3: Data Collection Overview

Data Collected	Enrollment	Implant	Follow Up		
			First (30 ~ 100 days) Office	12-Month (365 ± 30 days) Office/Phone	Additional Office/Phone
Informed Consent	X				
Inclusion/Exclusion	X				
Demographic data	X				
Medical History	X				
LAA imaging (TEE/CT/MRI)	X[a,b]	X[a]	X	X[a]	X[a]
Medication Regimen	X	X	X	X	X
Current status and Vital Signs	X	X	X	X	X
Adverse Event and Device Deficiency Reporting	*X*	*X*	*X*	*X*	*X*

[a] collected only if performed
[b] within 3 calendar days prior to implant

11.2. *Informed Consent*

In order to determine eligibility of a subject, the investigator needs to implement the consent process and verify and document the subject meets the inclusion/exclusion criteria. Informed consent is required from all patients (or their legal representatives) prior to the patient's participation in the study. The patient should be given ample time to consider participation and ask questions if necessary. An approved informed consent form shall be signed and personally dated by the subject (or legal representative). The original, signed document is to be kept with the subject's file and a copy must be provided to the subject.

11.3. *Enrollment Visit*

Only those subjects who provide consent and meet all of the study enrolment criteria may be enrolled and will have baseline data collected. Subjects who provide informed consent but do not meet all of the study enrolment criteria will be considered Consent Ineligible.

The data collection at Enrollment Visit includes:

- Demographic data, including: age at time of consent, gender, and ethnic;
- Risk factors, including those used to calculate HAS-BLED, $CHADS_2$ and CHA_2DS_2-VASc scores;
- Medical and cardiac history, including: cardiovascular diseases; prior history of ischemic stroke, hemorrhagic stroke or TIA; previous cardiac procedures; history of bleeding; indication for LAA occlusion;

- Current medical status; vital signs; AF status (paroxysmal, persistent, permanent);
- Current medication regimen for the use of antiplatelet and anticoagulation medications;
- Adverse Events and Device Deficiency, if applicable.

11.4. *LAA Imaging (e.g. TEE/CT/MRI)*

Prior to implantation with the WATCHMAN FLX device, an Enrollment TEE (or alternative imaging method) is a clinical standard to confirm there is no thrombus in the LAA or left atrium. If an intracardiac thrombus is visualized by echocardiographic imaging, the patients will not be implanted. Re-assessment may be scheduled per physician's discretion.

The Implant LAA imaging will also allow the investigator to obtain proper measurements of the LAA to correctly size the device, confirm device release criteria are met prior to device release, and to confirm adverse events have not occurred during the implant procedure (i.e., pericardial effusion). If an intracardiac thrombus is visualized by echocardiographic imaging, the patients will not be implanted. Re-assessment may be scheduled per physician's discretion.

The Follow-up LAA imaging is a clinical standard after the WATCHMAN FLX procedure, it is conducted to assess flow through and around the WATCHMAN FLX device, to ensure sealing and to verify there is no thrombus on the surface of the device prior to stopping dual platelet inhibition or warfarin. Additional LAA imaging may be conducted at the discretion of the investigator and according to center's practice.

Certain information from TEE/CT/MRI conducted during the course of the study will be captured on the study case report forms, including: heart rhythm; valve status; pericardial status; atrial septum characteristics; LAA size and type of anatomy; thrombus assessment.

For measurement of per-device flow:

- Use multiple TEE views (0°, 45°, 90°, and 135°) or 3D-TEE
- Echo colour Doppler TEE: set Nyquist limit to detect low velocity flow (20–30 cm/s). If leak is present, measure only the mosaic (high-velocity) colour of a communicating flow in multiple projections
- Use same settings during implantation and follow-up
- Document largest measurement as size of leak and achieved angle of measurement by TEE or CT/MRI

11.5. *Implant Procedure*

The implant procedure should be performed using standard of care methods established by the investigational center (e.g. sterile technique, personnel requirements, etc.). Implantation of the WATCHMAN FLX LAA Closure Device should only be performed by physicians trained in percutaneous and transseptal procedures who have completed the WATCHMAN FLX training program. Refer to the WATCHMAN FLX LAA Closure Technology Directions for Use for detailed instructions regarding the implantation and use of the WATCHMAN FLX technology. The following will be assessed during implant procedure and documented on case report forms for enrolled subjects:

- WATCHMAN FLX Device and Access System usage information, including device size and compression post-implant, procedure time (from first sheath inserted to last sheath removed);
- LAA imaging (as described in section 11.4): LAA measurements; intracardiac thrombus, device position, LAA seal, thrombus on the device surface;
- Concomitant procedures;
- Current medical status; vital signs; AF status;
- Current medication regimen for the use of antiplatelet and anticoagulation medications;
- Serious adverse events,adverse events and device deficiencies during implant procedure. Data to be collected for peri-procedural complications include, but are not limited to:
    - Cardiovascular events: pericardial effusion, cardiac tamponade, bleeding, stroke (ischemic/non-ischemic), TIA, systemic embolism (please refer to Appendix A for definitions of stroke/TIA and classification of bleeding events)
    - ICU: Length of stay
    - Conventional care unit: Length of stay
    - Device/procedure related complications

11.6. *Follow-up Procedures*

Subjects are expected to be followed at First (30 ~ 100 days) and 12-Month post-implant or until the study is terminated. An intermediate visit may be scheduled in a number of patients, per physician discretion. For subjects who are not scheduled to visit the clinic for a follow-up, a subject contact (e.g. phone call) will ensure capture of the endpoint related information, however it is recommended to perform an office visit for at least the First Follow-up visit.

i) In-Hospital Visit

The following will be assessed during each in-hospital visit and documented on case report forms for enrolled subjects:

- Current medication regimen for the use of antiplatelet and anticoagulation medications;
- Procedures performed since last visit;
- Current medical status; vital signs; AF status;
- LAA imaging (as described in section 11.4): device position, LAA seal, thrombus on the device surface, intracardiac thrombus and residual atrial septal shunt;
- Serious adverse events, adverse events and device deficiencies experienced since last visit. Data to be collected include, but are not limited to (please refer to Appendix A for definitions of stroke/TIA and classification of bleeding events):
    - ER admission due to WATCHMAN FLX implant related clinical events (stroke/TIA (ischemic/non-ischemic), systemic embolism, major and minor bleeding)

- Hospitalization (ICU and Ward) due to WATCHMAN FLX implant related clinical events (stroke/TIA (ischemic/non-ischemic), systemic embolism, major and minor bleeding)
- Specialist visits due to WATCHMAN FLX implant related clinical events (stroke/TIA (ischemic/non-ischemic), systemic embolism, major and minor bleeding)
- Diagnostic procedure following a clinical event related to WATCHMAN FLX (stroke/TIA (ischemic/non-ischemic), systemic embolism, major and minor bleeding)

ii) Subject Contact

For subjects who are not scheduled to visit the clinic for a follow-up, a subject contact (e.g. phone call) will ensure capture of the endpoint related information. The following will be assessed during each subject contact and documented on case report forms for enrolled subjects:

- Current medication regimen for the use of antiplatelet and anticoagulation medications
- Serious adverse events, adverse events and device deficiencies experienced since last visit. Data to be collected include, but are not limited to (please refer to Appendix A for definitions of stroke/TIA and classification of bleeding events):

  - ER admission due to WATCHMAN FLX implant related clinical events (stroke/TIA (ischemic/non-ischemic), systemic embolism, major and minor bleeding)
  - Hospitalization (ICU and Ward) due to WATCHMAN FLX implant related clinical events (stroke/TIA (ischemic/non-ischemic), systemic embolism, major and minor bleeding)
  - Specialist visits due to WATCHMAN FLX implant related clinical events (stroke/TIA (ischemic/non-ischemic), systemic embolism, major and minor bleeding)
  - Diagnostic procedure following a clinical event related to WATCHMAN FLX (stroke/TIA (ischemic/non-ischemic), systemic embolism, major and minor bleeding)

11.7. *Study Completion*

Each subject will be followed for 12 months after the implant. In case of premature termination of the study, data collection will stop accordingly. As this is an observational study, subjects will be managed according to standard of care as per centers practice following termination/completion of the study.

11.8. *Source Documents*

Printed, optical or electronic document containing source data shall be used; examples include hospital records, laboratory notes, device accountability records, radiographs, records kept at the investigation site, and at the laboratories involved in the clinical study.

Where copies of the original source document as well as printouts of original electronic source documents are retained, these shall be signed and dated by a member of the investigation center team with a statement that it is a true reproduction of the original source document.

12. Statistical Considerations

An overview of the study design, sample size and statistical analysis is provided below.

12.1. *Sample Size Justification*

This is a prospective, non-randomized, multi-center observational study with no formal pre-specified hypothesis test. All subjects will be followed for up to 12 months or until the study is terminated.

A sample size of up to 50 subjects was chosen to observe the safety and effectiveness of the WATCHMAN FLX™ Left Atrial Appendage Closure (LAAC) Device for subjects with non-valvular atrial fibrillation to reduce the risk of stroke in Hong Kong area.

The ongoing PINNACLE FLX study is designed to establish the safety and effectiveness of the WATCHMAN FLX™ Left Atrial Appendage Closure (LAAC) Device for subjects with non-valvular atrial fibrillation. The study has enrolled 398 subjects, and each subject will be followed for 2 years. However, the PINNACLE FLX study is conducted exclusively in the U.S. Although it is assumed that ethnic difference might not play an important role in the performance of the left atrial appendage closure, a small sample size study in Hong Kong should be able to provide valuable information supporting this assumption.

12.2. *Statistical Analysis and Data Sets*

There is no hypotheses testing in this small sample size observational study.

The Primary Effectiveness Endpoint is the occurrence of non-effective LAA closure defined as any peri-device flow > 5mm demonstrated by TEE/CT/MRI at First Follow-up.

The Primary Safety Endpoint is the occurrence of one of the following events between the time of implant and within 7 days following the procedure or by hospital discharge, whichever is later: all-cause death, ischemic stroke, systemic embolism, or device- or procedure-related events requiring open cardiac surgery or major endovascular intervention such as pseudoaneurysm repair, AV fistula repair, or other major endovascular repair. Percutaneous catheter drainage of pericardial effusions, snaring of an embolized device, thrombin injection to treat femoral pseudoaneurysm and nonsurgical treatments of access site complications are excluded from this endpoint.

Roll-in subjects are excluded from all Primary Endpoint analyses, and will be treated separately analysis set for the Primary Effectiveness analysis includes implanted subjects with a completed First Follow-up visit. The analysis set for the Primary Safety analyses will be the “intent-to-treat” analysis set, including implanted or attempted subjects. It is estimated that both Primary Effectiveness analysis and Primary Safety analysis dataset will include at least 40 subjects.

For the Primary Effectiveness Endpoint, it might be considered reasonable if up to 3 primary effectiveness endpoint events should occur in this small sample size study.

For the Primary Safety Endpoint, it might be considered reasonable if up to 3 primary safety endpoint events should occur in this small sample size study.

Missing data will not be dealt with systematically in this small sample size study. A tipping-point analysis might be conducted for the Primary Effectiveness Endpoint to assess the impact of different assumptions about the missing data on interpretation of the results.

For Secondary Endpoint and additional analysis, different data sets could be used exploratively.

While no formal hypothesis tests will be performed, descriptive statistics will be generated for the data collected at enrollment, during the implant procedure and at follow-up. For continuous variables, the mean, standard deviation, median, range and 95% confidence intervals will be reported. Confidence intervals (95%) for the difference between means will be used to compare groups. For proportions, 95% confidence intervals will be reported. For time-to-event analyses, all subjects not having an event or lost to follow-up will be censored at the time of the last documented follow-up visit.

For a sample size of 50, the 95% CIs of the rates for 0~5 events are as follows (exact methods), Table 4:

Table 4: 95% confidence interval for 0~5 events

Events	Rates (n=50)	Lower 95% CI	Upper 95% CI
0	0%	0.0%	7.1%
1	2%	0.1%	10.6%
2	4%	0.5%	13.7%
3	6%	1.3%	16.5%
4	8%	2.2%	19.2%
5	10%	3.3%	21.8%

Although not powered in the small sample study, explorative analyses may include, but will not be limited to the study endpoints. A variety of methods may be utilized in order to assess associations between the likelihood of each of the study endpoints and the patient and procedural characteristics outlined below. Covariates will be chosen for inclusion in the models based on the number of patients with complete data for each outcome according to the prioritization in Table 5**.**

Methods to model multivariate associations may include but are not limited to the following:

1) Univariate analysis of individual predictors, and subsequent construction of multivariate logistic regression models incorporating all significant univariate predictors.

2) Parsimonious multivariate logistic regression models constructed through stepwise selection algorithm.

3) Classification and regression tree models.

Table 5: Covariates of Interest

1. Age ≥ 80 years
2. Gender
3. Type of AF (paroxysmal; persistent; permanent)
4. Previous Stroke/TIA
5. Previous major bleeding event
6. HASBLED ≥ 3
7. $CHADS_2 \geq 3$
8. CHA_2DS_2-VASc ≥ 5
9. Type of anticoagulation therapy (Warfarin; NOACs; antiplatelet)
10. Multiple concomitant procedures vs watchman implant only

13. Data Management

13.1. *Data Collection, Processing, and Review*

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

The clinical database will reside on a production server hosted by Medidata. All changes made to the clinical data will be captured in an electronic audit trail and available for review by Boston Scientific Corporation (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 the sponsor require a new electronic signature by the Investigator acknowledging and approving the changes.

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

13.2. *Data Retention*

The Investigator will maintain, at the investigative site, in original format all essential study documents and source documentation that support the data collected on the study subjects in compliance with ICH/GCP guidelines. Documents must be retained for at least 2 years after the last approval of a marketing application or until at least 2 years have elapsed since the

formal discontinuation study. These documents will be retained for a longer period of time by agreement with BSC or in compliance with other local regulations. It is BSC's responsibility to inform the Investigator when these documents no longer need to be maintained. The Investigator will take measures to ensure that these essential documents are not accidentally damaged or destroyed. If for any reason the Investigator withdraws responsibility for maintaining these essential documents, custody must be transferred to an individual who will assume responsibility and BSC must receive written notification of this custodial change.

14. Amendments

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

15. Deviations

An Investigator must not make any changes or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency. An investigator shall notify the sponsor and the reviewing IRB/EC of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency, and those deviations which affect the scientific integrity of the clinical investigation.

All deviations from the investigational plan, with the reason for the deviation and the date of occurrence, must be documented and reported to the sponsor within 14 days using the appropriate EDC eCRF. Sites may also be required to report deviations to the IRB/EC, per local guidelines and government regulations.

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

16. Compliance

16.1. *Statement of Compliance*

This study will be conducted in accordance with ISO 14155:2011 Clinical Investigation of Medical Devices for Human Subjects-Good Clinical Practice, or the relevant parts of the ICH Guidelines for Good Clinical Practice, ethical principles that have their origins in the Declaration of Helsinki, and pertinent individual country laws and regulations. The study shall not begin until the required approval/favorable opinion from the Ethics Committee and/or regulatory authority has been obtained, if appropriate. Any additional requirements imposed by the EC or regulatory authority shall be followed, if appropriate.

16.2. *Investigator Responsibilities*

The Principal Investigator of an investigational center is responsible for ensuring that the study is conducted in accordance with the Clinical Study Agreement, the investigational

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

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

- Prior to beginning the study, sign the Investigator Agreement and Protocol Signature page documenting his/her agreement to conduct the study in accordance with the protocol.
- Provide his/her qualifications and experience to assume responsibility for the proper conduct of the study and that of key members of the center team through up-to-date curriculum vitae or other relevant documentation and disclose potential conflicts of interest, including financial, that may interfere with the conduct of the clinical study or interpretation of results.
- Make no changes in or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency; document and explain any deviation from the approved protocol that occurred during the course of the clinical investigation.
- Create and maintain source documents throughout the clinical study and ensure their availability with direct access during monitoring visits or audits; ensure that all clinical-investigation-related records are retained per requirements.
- Ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.
- Record, report, and assess (seriousness and relationship to the device/procedure) every adverse event and observed device deficiency.
- Report to BSC, per the protocol requirements, all AEs,ADEs, SAEs, SADEs, UADEs, USADEs and device deficiencies that could have led to a SADE and potential/USADE or UADE.
- Report to the IRB/EC and regulatory authorities any SAEs and device deficiencies that could have led to a SADE and potential/USADE or UADE, if required by the national regulations or this protocol or by the IRB/EC, and supply BSC with any additional requested information related to the safety reporting of a particular event.
- Allow the sponsor to perform monitoring and auditing activities, and be accessible to the monitor and respond to questions during monitoring visits.
- Allow and support regulatory authorities and the IRB/EC when performing auditing activities.
- Ensure that informed consent is obtained in accordance with applicable laws, this protocol and local IRB/EC requirements.
- Provide adequate medical care to a subject during and after a subject's participation in a clinical study in the case of adverse events, as described in the Informed Consent Form (ICF).
- Inform the subject of the nature and possible cause of any adverse events experienced.

- Inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required.
- Provide the subject with well-defined procedures for possible emergency situations related to the clinical study, and make the necessary arrangements for emergency treatment, ensure that clinical medical records are clearly marked to indicate that the subject is enrolled in this clinical study.
- Ensure that, if appropriate, subjects enrolled in the clinical investigation are provided with some means of showing their participation in the clinical investigation, together with identification and compliance information for concomitant treatment measures (contact address and telephone numbers shall be provided).
- Inform, with the subject's approval or when required by national regulations, the subject's personal physician about the subject's participation in the clinical investigation.
- Make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from clinical investigation while fully respecting the subject's rights.
- Ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation.
- Ensure that maintenance and calibration of the equipment relevant for the assessment of the clinical investigation is appropriately performed and documented, where applicable.

16.2.1. Delegation of Responsibility

When specific tasks are delegated by an investigator, included but not limited to conducting the informed consent process, the investigator is responsible for providing appropriate training and adequate supervision of those to whom tasks are delegated. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

16.2.2. Investigator Records

The investigator is responsible for the preparation (review and signature) and retention of the records cited below. Records are subject to inspection and must be retained for a period of at least two (2) years (or according to local regulatory requirements) after the investigation is terminated or the date that the records are no longer required for purposes of supporting publications or regulatory submissions.

- All significant correspondence which pertains to the investigation
- Subjects' case history records, including: signed subject informed consent form; all relevant observations; observations of adverse device events; medical history; completed sponsor Case Report Forms; documentation of the dates and reasons for any deviation from the protocol
- Copies of Case Report Forms and clinical data

- Signed Investigator Agreement and recent curriculum vitae, both of which also must be submitted to the sponsor
- IRB/EC approval and discourse documentation. A copy of the IRB/EC approval must be submitted to the sponsor

16.3. *Institutional Review Board/ Ethics Committee*

A copy of the protocol, proposed Informed Consent form, other written subject information, and any proposed advertising material must be submitted to the EC for written approval. A copy of the written EC approval of the protocol and Informed Consent form must be received by the sponsor before recruitment of subjects into the study and shipment of investigational product.

The Investigator must submit and, where necessary, obtain approval from the EC for all subsequent protocol amendments and changes to the Informed Consent form. The Investigator must notify the EC of deviations from the protocol or SAEs and SADEs occurring at the site in accordance with local procedures.

The Investigator is responsible for obtaining annual EC approval and renewal throughout the duration of the study. Copies of the Investigator's reports and the EC continuance of approval must be sent to the sponsor.

16.4. *Sponsor Responsibilities*

All information and data sent to BSC concerning subjects or their participation in this study will be considered confidential by BSC. Only authorized BSC personnel or a BSC representative will have access to these confidential records. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this study. Study data collected during this study may be used by BSC for the purposes of this study, publication, and to support future research and/or other business purposes. All data used in the analysis and reporting of this study will be without identifiable reference to specific subject name.

Boston Scientific will keep subjects' health information confidential in accordance with all applicable laws and regulations. Boston Scientific may use subjects' health information to conduct this study, as well as for additional purposes, such as overseeing and improving the performance of its device, new medical research and proposals for developing new medical products or procedures, and other business purposes. Information received during the study will not be used to market to subjects; subject names will not be placed on any mailing lists or sold to anyone for marketing purposes.

16.4.1. Sponsor Records

The sponsor will maintain the following records:

- All correspondence which pertains to the investigation
- Signed investigator agreements and curriculum vitae
- System/procedure related Adverse Device Events

- All case report forms, including samples of subject informed consents, submitted by the investigator; investigational plan and report of prior investigations
- Hospital staff training and study visit reports
- The sponsor will own and store the clinical data generated under this protocol

16.5. *Insurance*

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

17. Monitoring

Monitoring (on-site and remote) will be performed during the study to assess continued compliance with the protocol and applicable regulations. In addition, the 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 Investigator continues to have sufficient staff and facilities to conduct the study safely and effectively. The Investigator/institution guarantees direct access to original or electronic source documents by BSC personnel, their designees, and appropriate regulatory authorities.

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

18. Potential Risks and Benefits

18.1. *Risks Associated with the study*

Patients enrolled in this study will not be exposed to any additional testing, procedures or risks as compared to patients who are routinely implanted with the WATCHMAN FLX device and not enrolled in this study. The study only collects data from procedures and visits that are performed as routine practice, based on the patient's clinical indications

18.2. *Risks Associated with a standard WATCHMAN FLX Implant & Procedure*

Even if the WATCHMAN FLX implant is performed as part of clinical practice, for completeness of information we report here the section of the WATCHMAN FLX Directions For Use listing the possible adverse events and possible adverse device effects associated with implantation of a WATCHMAN FLX device, in alphabetical order:

- Air embolism
- Airway trauma
- Allergic reaction to contrast media/medications or device materials
- Altered mental status
- Anemia requiring transfusion

- Anesthesia risks
- Angina
- Anoxic encephalopathy
- Arrhythmias
- Atrial septal defect
- AV fistula
- Bruising, hematoma, or seroma
- Cardiac perforation
- Chest pain/discomfort
- Confusion post procedure
- Congestive heart failure
- Contrast related nephropathy
- Cranial bleed
- Decreased hemoglobin
- Deep vein thrombosis
- Death
- Device embolism
- Device fracture
- Device thrombosis
- Edema
- Embolism
- Excessive bleeding
- Fever
- 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
- Nausea
- Oral bleeding
- Pericardial effusion/tamponade
- Pleural effusion
- Prolonged bleeding from a laceration
- Pseudoaneurysm
- Pulmonary edema
- Renal failure

- Respiratory insufficiency/failure
- Stroke - Hemorrhagic
- Stroke - Ischemic
- Surgical removal of the device
- TEE complications (throat pain, bleeding, esophageal trauma)
- Thrombocytopenia
- Thrombosis
- Transient ischemic attack (TIA)
- Valvular damage

There may be other potential adverse events that are unforeseen at this time.

Some additional events that may be expected in catheterization procedures include:

- Pneumothorax
- Pulmonary Vein Obstruction
- Valvular or vascular damage

18.3. *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 procedures and/or follow-ups and by promptly supplying BSC with all pertinent information required by this protocol.

18.4. *Anticipated Benefits*

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

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

19. Informed Consent

Subject participation in this clinical study is voluntary. Informed Consent is required from all subjects or their legally authorized representative. The Investigator is responsible for ensuring that Informed Consent is obtained prior to any 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 body, as applicable. The ICF must be approved by the center’s IRB, or central IRB, if applicable.

Boston Scientific will provide a study-specific template of the ICF to investigators participating in this study. The ICF template may be modified to meet the requirements of the investigative center's EC and local regulations. Any modification requires approval from BSC, or its representative, 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 EC approval prior to their use. Privacy language shall be included in the body of the form or as a separate form as applicable.

The process of obtaining Informed Consent shall:

- 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 and by the investigator or an authorized designee responsible for conducting the informed consent process. If a legal representative signs, the subject shall be asked to provide informed consent for continued participation as soon as his/her medical condition allows. The original signed ICF will be retained by the 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 body according to their requirements (e.g., FDA requirement is within 5 working days of learning of such an event). Any violations of the informed consent process must be reported as deviations to the sponsor and local regulatory authorities, 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 protocol, a change in Principal Investigator, administrative changes, or following annual review by the IRB. The new version of the ICF must be approved by the IRB/EC. Boston Scientific approval is required if changes to the revised ICF are requested by the center's IRB/EC. The IRB/EC will determine the subject population to be re-consented.

20. Safety Reporting

Adverse event definitions are provided in **Table 6.**

Table 6: Adverse Event Definitions

Term	Definition
Adverse Event (AE) *Ref: ISO 14155-2011* *Ref: MEDDEV 2.7/3 12/2010*	Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, whether or not related to the investigational medical device. NOTE 1: This includes events related to the investigational medical device or comparator. NOTE 2: This definition includes events related to the procedures involved (any procedure in the clinical investigation plan). NOTE 3: For users or other persons, this definition is restricted to events related to the investigational medical device.
Adverse Device Effect (ADE) *Ref: ISO 14155-2011* *Ref: MEDDEV 2.7/3 12/2010*	Adverse event related to the use of an investigational medical device NOTE 1: This definition includes any adverse event resulting from insufficient or inadequate instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device. NOTE 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.
Serious Adverse Event (SAE) *Ref: ISO 14155-2011* *Ref: MEDDEV 2.7/3 12/2010*	Adverse event that: a) Led to death, b) Led to serious deterioration in the health of the subject, that either resulted in: o a life-threatening illness or injury, or o a permanent impairment of a body structure or a body function, or o in-patient or prolonged hospitalization 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 c) Led to fetal distress, fetal death, or a congenital abnormality or birth defect. **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.
Serious Adverse Device Effect (SADE) *Ref: ISO 14155-2011* *Ref: MEDDEV 2.7/3 12/2010*	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated Adverse Device Effect (UADE)	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect,

Table 6: Adverse Event Definitions

Term	Definition
Ref: 21 CFR Part 812	problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.
Unanticipated Serious Adverse Device Effect (USADE) *Ref: ISO 14155-2011* *Ref: MEDDEV 2.7/3 12/2010*	Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the System Guide of each device model **NOTE 1**: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the current version of the System Guide of each device model
Device Deficiency *Ref: ISO 14155-2011* *Ref: MEDDEV 2.7/3 12/2010*	A device deficiency is any inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. **NOTE 1**: Device deficiencies include malfunctions, misuse or use errors, and inadequate labeling.

Abbreviations: EC=Ethics Committee; IRB=Institutional Review Board

Table 7: Criteria for Assessing Relationship of Study Device or Procedure to Adverse Event

Table 7: Criteria for Assessing Relationship of Study device/Procedure to Adverse Event

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

Table 7: Criteria for Assessing Relationship of Study device/Procedure to Adverse Event

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

20.1. *Investigator Reporting Requirements*

When reporting an Adverse Event the investigator will indicate the diagnosis of the event and correlating signs and symptoms on the adverse event case report form. Individual signs and symptoms and treatment/intervention/diagnostic testing should not be reported as separate adverse events, instead be reported as supporting documentation on the AE CRF. Additionally, it is not necessary to report an underlying disease that was present at baseline (i.e., CHF, AF, hypertension, chronic anemia, etc.). However, any increase in the severity of the underlying disease may require reporting, if at the determination of the investigator, it is relevant to the study. If possible, death should not be recorded as an AE, but should only be reflected as an outcome of a specific SAE (see Table 66 for AE definitions).

In-patient hospitalization is defined as the subjects being admitted to the hospital, with the following exceptions.

- A hospitalization that is uncomplicated and elective/planned (i.e., planned prior to enrollment) does not have to be reported as an SAE.
- If complications or AEs occur during an elective/planned (i.e., planned prior to enrollment) hospitalization after enrollment, the complications and AEs must be reported as AEs or SAEs if they meet the protocol-specified definitions. However, the original elective/planned hospitalization(s) itself should not be reported as an SAE.

Adverse experiences that require reporting by the investigator to the sponsor include any adverse event with clinical symptoms that could possibly be contributed to any of the following:

- The WATCHMAN FLX device;
- The WATCHMAN FLX implant procedure;
- The use of medications including warfarin, or other equivalent oral anticoagulant per institution's protocol, clopidogrel or aspirin (i.e., gastrointestinal bleeding due to warfarin or an allergic reaction to clopidogrel);
- Any WATCHMAN FLX related procedures (i.e., clinical complications from TEE or other procedure required by labeling)

The following adverse events will also be reported:

- Neurological events including, but not limited to, stroke, TIA or seizure which are not pre-study conditions
- Any events possibly related to stroke/TIA, systemic embolization, death, etc.
- Thrombosis
- Bleeding complications requiring intervention or transfusion of blood.

Please refer to 错误!未找到引用源。 for definitions of stroke/TIA and classification of bleeding events. Each adverse event will be evaluated by the investigator for relatedness and seriousness.
The communication requirements for reporting to BSC are as shown in **Table :**

Table 8: Investigator Reporting Requirements

Event Classification	Communication Method	Communication Timeline
Unanticipated Adverse Device Effect /Unanticipated Serious Adverse Device Effect	Complete AE eCRF page with all available new and updated information. Provide all relevant source documentation (unidentified) for reported event	d) Within 24hours of first becoming aware of the event. e) Terminating at the end of the study
Serious Adverse Event including Serious Adverse Device Effects	Complete AE eCRF page with all available new and updated information	f) Within 24 hours of first becoming aware of the event or as per local/regional regulations. g) Reporting required through the end of the study
	Provide all relevant source documentation (unidentified) for reported event if required by medical reviewer.	h) When documentation is available
Adverse Event including Adverse Device Effects	Complete AE eCRF page, which contains such information as date of AE, treatment of AE resolution,	i) No later than 10 working days after becoming aware of the information

Table 8: Investigator Reporting Requirements

Event Classification	Communication Method	Communication Timeline
	assessment of seriousness and relationship to the device	j) Reporting required through the end of the study.
Device Deficiencies (including but not limited to failures, malfunctions, and product nonconformities) Note: Any Investigational Device Deficiency that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable event.	Complete applicable Device Deficiency CRF page with all available new and updated information. Provide all relevant source documentation (unidentified) for reported event if required by medical reviewer.	k) Investigators should report within 24hours of first becoming aware of the event and as per local/regional regulations l) Reporting required through the end of the study

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

20.2. *Boston Scientific Device Deficiencies*

All device deficiencies will be documented and reported to BSC on the appropriate eCRF within 24hours of first becoming aware of the event. Device deficiencies are not to be reported as adverse events. However, if there is an adverse event that results from a device deficiency, that specific event would be recorded on the appropriate eCRF. If possible, the device(s) should be returned to BSC for analysis. If it is not possible to return the device, the investigator should document why the device was not returned and the final disposition of the device. Device deficiencies should also be documented in the subject's medical record.

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

BSC is responsible for reporting serious adverse event and device deficiency information to all participating investigators and regulatory authorities, as applicable. The Principal Investigator is responsible for informing the IRB/EC, and regulatory authorities of U(S)ADE and SAE as per local/regional requirements.

BSC shall notify all participating study centers if SAEs/SADEs and device deficiency 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 demands changes to the protocol or the conduct of the study in order to further minimize the unanticipated risks.

21. Committees

21.1. *Safety Monitoring Process*

The BSC Medical Safety group will provide safety oversight and classify individual events. During regularly scheduled monitoring visits, clinical research monitors will support the dynamic reporting process through their review of source document information.

The BSC Medical Safety group includes physicians with expertise in Electrophysiology (EP), and/ or Cardiology, as well as other healthcare professionals with the necessary therapeutic and subject matter expertise to evaluate and classify the events into the categories outlined above.

22. Suspension or Termination

This study may be terminated at any time. Upon completion or termination, all data must be returned to the sponsor.

23. Publication Policy

The results of this study may be submitted in the form of abstracts to international and/or national congresses and/or in the form of publications to scientific journals. Publication policy will be, at a minimum, dependent on the number of complete patient datasets per site. Boston Scientific is committed to supporting publication of results of Boston Scientific-sponsored clinical research investigations in written or oral publications. Boston Scientific shall do its best to support proposals for sub-analysis and to include as many participating investigators despite the fact that authorship cannot be guaranteed. Therefore clinical investigators are encouraged to identify topics of interest and initiate publications on their own or the pooled data. This will be done in close cooperation with the Sponsor and with the International Study Chairman or/and an Executive committee, if any has been defined. No abstract(s) or article(s) can be submitted for publication without prior authorization from the Sponsor. In accordance with the Corporate Policy on the Conduct of Human Subject Research, Boston Scientific requires disclosure of its involvement as a sponsor or financial supporter in any publication or presentation relating to a Boston Scientific study or its results. In accordance with the Corporate Policy for the Conduct of Human Subject Research, Boston Scientific will submit study results for publication (regardless of study outcome) following the conclusion or termination of the study. Boston Scientific Corporation adheres to the Contributorship Criteria set forth in the Uniform Requirements of the International Committee of Medical Journal Editors (ICMJE; http://www.icmje.org). In order to ensure the public disclosure of study results in a timely manner, while maintaining an unbiased presentation of study outcomes, Boston Scientific 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.

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25. Abbreviations and Definitions

25.1. *Definitions*

25.1.1. Stroke/TIA definitions

Broad definitions:

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

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

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

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

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

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

Stroke diagnostic criteria:

- Rapid onset of a focal or global neurological deficit with at least one of the following: change in level of consciousness, hemiplegia, hemiparesis, numbness or sensory loss affecting one side of the body, dysphasia or aphasia, haemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke;
- Duration of a focal or global neurological deficit ≥24 h; OR, 24 h, if therapeutic intervention(s) were performed (e.g. thrombolytic therapy or intracranial angioplasty); OR available neuroimaging documents a new haemorrhage or infarct; OR the neurological deficit results in death
- No other readily identifiable non-stroke cause for the clinical presentation (e.g. brain tumor, trauma, infection, hypoglycaemia, peripheral lesion, pharmacological influences)
- Confirmation of the diagnosis by at least one of the following:
    - Neurology or neurosurgical specialist
    - Neuroimaging procedure (MR or CT scan or cerebral angiography)
    - Lumbar puncture (i.e. spinal fluid analysis diagnostic of intracranial haemorrhage)

Stroke Types:

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

Hemorrhagic:

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

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

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

Not otherwise specified: an episode of acute neurological dysfunction presumed to be caused by ischemia or hemorrhage, persisting ≥ 24 hours or until death, but without sufficient evidence to be classified as one of the above

(from Kappetein, A.P., et al., J Am Coll Cardiol, 2012. **60**(15): p. 1438-54)

25.1.2. Classification of Bleeding events

In response to the need to develop, disseminate, and ultimately adopt standardized bleeding end-point definitions for subjects receiving antithrombotic therapy, the Bleeding Academic

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

Type 0:
No bleeding

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

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

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

Type 3:

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

Type 3b:
- Overt bleeding plus hemoglobin drop ≥5 g/dL* (provided hemoglobin drop is related to bleed),
- Cardiac tamponade,
- Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid),
- Bleeding requiring intravenous vasoactive agents

Type 3c:
- Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal),
- Subcategories confirmed by autopsy or imaging or lumbar puncture,
- Intraocular bleed compromising vision.

Type 4:
- CABG-related bleeding,
- Perioperative intracranial bleeding within 48 h,
- Reoperation after closure of sternotomy for the purpose of controlling bleeding
- Transfusion of ≥ 5 U whole blood or packed red blood cells within a 48-h period,

- Chest tube output more than or equal to 2L within a 24-h period

Type 5:

Fatal bleeding

Type 5a:

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

Type 5b:

Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

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

For the purposes of the HK FLX trial, a BARC score of Type 3 a, b, c and 5 a and b will be considered a major bleed.