

# EWOLUTION

REgistry on WATCHMAN Outcomes in Real-Life Utilization

## Clinical Protocol

07-13

### Sponsored By:

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## 2. Protocol Synopsis

<b>EWOLUTION - REgistry on <u>W</u>ATCHMAN <u>O</u>utcomes in Real-<u>L</u>ife <u>U</u>tilization</b>	
Objective(s)	<ul style="list-style-type: none"> <li>• To compile real-world clinical outcomes data for WATCHMAN LAA (Left Atrial Appendage) Closure Technology in patients who are implanted with the WATCHMAN device in a commercial clinical setting.</li> <li>• To collect real-world usage data that may be needed for reimbursement of WATCHMAN technology in certain countries.</li> </ul>
Marketing Performance Expectation	The WATCHMAN LAA Closure Technology is designed to prevent embolization of thrombi that may form in the LAA, thereby preventing the occurrence of ischemic stroke and systemic thromboembolism.
Test Device	WATCHMAN LAA Closure Technology
Device Sizes	21mm, 24mm, 27mm, 30mm, 33mm
Study Design	This is an observational, prospective, non-randomized, multicenter study.
Planned Number of Subjects	Approximately 1000 subjects will be enrolled in the study.
Planned Nr of Centers/Countries	Up to 70 sites in the International (Outside of US) region.
Primary Endpoint	Primary analyses may include, but will not be limited to, the following: procedural complications, incidence of stroke and death. Descriptive statistics will be used for baseline, procedure and follow-up data collected through the study.
Study Duration	Enrolment is expected to be completed in 21 months; therefore the total study duration is estimated to be 48 months.
Follow-up (FU) Schedule	<p>Each patient will be followed for a period of two years after enrolment according to the schedule and standard practice at the enrolling centers. There will be no additional visits, nor procedures, for subjects who participate in the study. Subjects are expected to be followed at implant, then at one post-implant visit (typically between 1-3 months of implant), and then annually through 2 years post implant. An intermediate visit may be a scheduled in a number of patients, per physician discretion. In order to reliably capture patient status at study end a FU window of <math>24 \pm 3</math> months will be considered acceptable for scheduling the last visit.</p> <p>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 in-office visit for at least the first annual visit.</p>

<b>EWOLUTION - Registry on WATCHMAN Outcomes in Real-Life Utilization</b>						
	<b>Data Collection Overview</b>					
	<b>Data Collected</b>	<b>BASELINE</b>	<b>IMPLANT</b>	<b>Follow Up</b>		
				<b>Post-implant Visit*</b>	<b>FU office visit</b>	<b>FU phone visit</b>
	Informed Consent	X				
	Inclusion/Exclusion	X				
	Demographic data	X				
	Medical History	X				
	LAA imaging (e.g. TEE)		X	X <sup>§</sup>	X <sup>**</sup>	
	Medication Regimen	X	X	X	X	X
	Current status and Vital Signs	X	X	X	X	
<i>Adverse Event Reporting</i>	<i>X</i>	<i>X</i>	<i>X</i>	<i>X</i>	<i>X</i>	
<p>*expected 1-3 month from implant depending on center's practice  <sup>§</sup> Control TEE/CT is clinical standard after the Watchman procedure to ensure sealing and exclude thrombus on the device prior to stop dual platelet inhibition or warfarin  ** collected only if performed, according to center's practice</p>						
Key Inclusion Criteria	<p>A subject may be enrolled in the study if all of the following inclusion criteria are met, provided no exclusion criteria are met:</p> <ol style="list-style-type: none"> <li>1. Patients who are eligible for a WATCHMAN device according to current international and local guidelines (and future revisions) and per physician discretion;</li> <li>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;</li> <li>3. Patients whose age is 18 years or above, or of legal age to give informed consent specific to state and national law.</li> </ol>					
Key Exclusion Criteria	<p>Subjects will be excluded from the study if they meet any of the following criteria:</p> <ol style="list-style-type: none"> <li>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.</li> <li>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);</li> </ol>					

<b>EWOLUTION - REgistry on WATCHMAN Outcomes in Real-Life Utilization</b>									
	3. The subject is unable or not willing to complete follow-up visits and examination for the duration of the study.								
<b>Statistical Methods</b>									
<b>Statistical Test Method</b>	No formal pre-specified hypotheses will be tested. However, a variety of statistical modeling methods may be utilized in order to assess associations between the likelihood of each of the three outcomes and the pre-specified patient and procedural characteristics, including multivariate logistic regression and classification and regression tree models.								
<b>Sample Size Parameters</b>	<p>This is a prospective, multicenter non-randomized observational study with no formal pre-specified hypothesis test. All subjects will be followed for up to 2 years or until the study is terminated.</p> <p>A sample size of up to 1000 subjects was chosen to assess incidence of rare events with a large degree of precision. The table below provides the two-sided 95% confidence interval assuming an event rate of 5%.</p> <p>Two-Sided Confidence Interval by Sample Size:</p> <table border="1" style="margin-left: auto; margin-right: auto;"> <thead> <tr> <th style="text-align: center;">Sample Size</th> <th style="text-align: center;">95% CI</th> </tr> </thead> <tbody> <tr> <td style="text-align: center;">500</td> <td style="text-align: center;">5% ± 1.9%</td> </tr> <tr> <td style="text-align: center;">750</td> <td style="text-align: center;">5% ± 1.6%</td> </tr> <tr> <td style="text-align: center;">1000</td> <td style="text-align: center;">5% ± 1.4%</td> </tr> </tbody> </table>	Sample Size	95% CI	500	5% ± 1.9%	750	5% ± 1.6%	1000	5% ± 1.4%
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## 4. Introduction

### i) 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 years<sup>1</sup>. 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<sup>2</sup>.

Treatment with warfarin therapy for the prevention of thromboemboli originating in the left atrial appendage has been well documented<sup>3-5</sup>. Warfarin therapy targeting an International Normalized Ratio (INR) between 2.0 – 3.0 is considered the gold standard treatment today 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 new oral anticoagulants (NOACs) which include dabigatran, rivaroxaban, apixaban. Unlike Warfarin, NOACs can be administered without the need for monitoring, have fewer food and drug interactions and provide an improved efficacy/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<sup>6-9</sup>. 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 vs warfarin, however, intracranial and fatal bleeding is less frequent with rivaroxaban<sup>10</sup>. 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<sup>11</sup>.

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 has developed the WATCHMAN<sup>®</sup> Left Atrial Appendage Closure (LAA) 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 may 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 WATCHMAN LAA Closure Technology in subjects with non-valvular AF.

### ii) WATCHMAN Therapy

The WATCHMAN® LAA Closure Technology is intended for patients with non-valvular atrial fibrillation who require treatment for potential thrombus formation.

The implanted component of the system, hereafter referred to as the WATCHMAN device, is an approved commercially available novel device designed to prevent the embolization of thrombi that may form in the LAA. The WATCHMAN device may prevent 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. The WATCHMAN device is manufactured by Boston Scientific, received CE Mark in October 2005, and is under IDE in the United States (U.S.).

### iii) WATCHMAN Clinical Study Experience

Clinical evaluation of the WATCHMAN LAA Closure Technology has been ongoing since 2002, with all U.S. studies conducted under IDE #G020312. **Table 1** lists the clinical studies conducted with the WATCHMAN device.

**Table 1: Clinical Studies of the WATCHMAN Device**

Study	Dates of Enrolment	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	Ongoing through 5 years
CAP Registry	Aug 2008 – Jun 2010	566	26	Ongoing through 5 years
ASAP (feasibility study)	Jan 2009 – Nov 2011	150	4	Ongoing through 2 years
PREVAIL (pivotal study)	Nov 2010 – Jun 2012	461	41	Ongoing through 5 years
CAP2 Registry	Sep 2012 - ongoing	Up to 1500	Up to 60	Ongoing through 5 years

The first pilot study demonstrated that the WATCHMAN device was safe and met the performance criteria for use in subjects with non-valvular atrial fibrillation.

The first pivotal study, WATCHMAN Left Atrial Appendage System for Embolic PROTECTION in Patients with Atrial Fibrillation<sup>12</sup> (PROTECT-AF), demonstrated non-

inferiority of the WATCHMAN device to long-term warfarin therapy for the primary efficacy endpoint of stroke, systemic embolism and cardiovascular death.

Most recent data analysis of The PROTECT AF<sup>13</sup> 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 efficacy 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 efficacy 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<sup>14</sup> (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.

The ASA Plavix Feasibility Study With WATCHMAN Left Atrial Appendage Closure Technology (ASAP) study was a feasibility study conducted in Europe to characterize the performance of the WATCHMAN device in non-valvular atrial fibrillation (AF) subjects with contraindications to warfarin therapy.

The Continued Access Protocol (CAP2) is 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.

## 5. Device Description

The WATCHMAN device is designed to be permanently implanted at or slightly distal to the ostium (opening) of the LAA to prevent embolization of blood clots formed within the trabeculated LAA. The placement procedure can be performed under general or

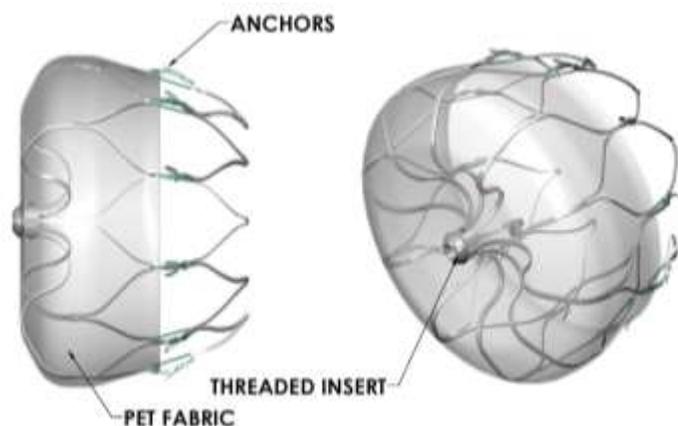
conscious sedation in a catheterization or electrophysiology (EP) laboratory setting using standard transseptal technique under fluoroscopic and echocardiographic guidance.

The WATCHMAN LAA Closure Technology is a three-component system which includes the WATCHMAN LAA Closure Device (WATCHMAN device), the WATCHMAN Delivery System and the WATCHMAN Access Sheath.

#### i) WATCHMAN Device

The WATCHMAN device is comprised of a self-expanding nitinol frame structure with fixation anchors around the device perimeter and a permeable polyester fabric that covers the atrial facing surface of the device (*Figure 1*). The device is constrained within the Delivery System until deployment into the LAA. The WATCHMAN device is available in various sizes to accommodate a range of LAA ostial diameters. The device size, measured in mm, is the diameter of the device at its maximum dimension in an uncompressed (fully expanded) state. An appropriate device size is selected based on LAA measurements obtained utilizing Fluoroscopy and Transesophageal Echocardiography (TEE).

*Figure 1: WATCHMAN Device*



#### ii) WATCHMAN Delivery System

The delivery catheter 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 12 French.

The WATCHMAN device is pre-loaded and is deployed by loosening the valve on the Delivery System and retracting the outer sheath. The WATCHMAN device can be partially recaptured and redeployed if the device is too distal. If the device is deployed too proximal, it can be fully recaptured. The device is released by rotating the device deployment knob counter clockwise.

### iii) WATCHMAN Access Sheath

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

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

## 6. Objectives

The objective of the study is to compile real world clinical data on the use of the WATCHMAN LAA Closure Technology in a commercial clinical setting.

The study aims to obtain additional clinical data on procedural success and complications, as well as information about long-term patient outcomes, including clinical data on incidence of stroke/TIA.

The collected real-world data may be needed for reimbursement of WATCHMAN technology in certain countries.

## 7. Endpoint Analysis

Primary analyses may include, but will not be limited to, the following: procedural complications, incidence of stroke and death. Descriptive statistics will be used for baseline, procedure and follow-up data collected through the study.

## 8. Design

This WATCHMAN Registry is an observational, prospective, non-randomized, multicenter study.

### 8.1. Scale and Duration

Approximately 1000 subjects will be enrolled at up to 70 sites in the International (Outside the US) region.

Each patient will be followed for a period of two years after implant according to the schedule. There will be no additional visits for subjects who participate in the study.

It is anticipated that enrolment will be conducted over a period of 21 months; therefore the total study duration is estimated to be 48 months.

## **8.2. *Justification for the Study Design***

This is a purely observational post-market data collection designed to compile real-world clinical outcomes data for WATCHMAN LAA Closure Technology. The implant of the device is done 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 Watchman 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 (no additional burden for the patient like additional invasive examination or additional follow-up).

## **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 9.2 and 9.3.

### **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 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. Enrolment**

Subjects who meet the eligibility criteria as per 9.2 and 9.3, have signed and dated the Informed Consent Form and actually undergo a WATCHMAN implant procedure are considered enrolled in the study. Baseline data from subjects who meet the eligibility criteria as per 9.2 and 9.3, have signed and dated the Informed Consent Form but do not eventually undergo a WATCHMAN implant procedure are collected for epidemiological reasons, to better characterize the population. The start of the WATCHMAN implant procedure is considered the insertion of the WATCHMAN Access Sheath.

### **10.2. Withdrawal**

Every effort should be made to retain subject enrolment 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 (please refer to Figure 2 for a summary)**

#### **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 enrolment 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 device will be classified as “**Intent**”. This definition includes subjects that do not meet echocardiographic criteria for a WATCHMAN implant at the implant TEE/CT 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.

Subjects who have been consented, but not yet implanted at the time of enrolment 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 enrolment 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 Access Sheath inserted to implant the device, but eventually does not receive a WATCHMAN device will be classified as “**Attempt**”. These subjects may be withdrawn, unless a re-implant of a study device is planned, per physician discretion. These subjects will be handled as “Implant” (see next section), if the re-implant is successful. Subjects who eventually have not received a WATCHMAN device at the time of enrolment 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 enrolment ceiling and will be used for analyses of the endpoints. The original signed Informed Consent must be maintained in the center’s study file and the following forms must be completed:

- 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.

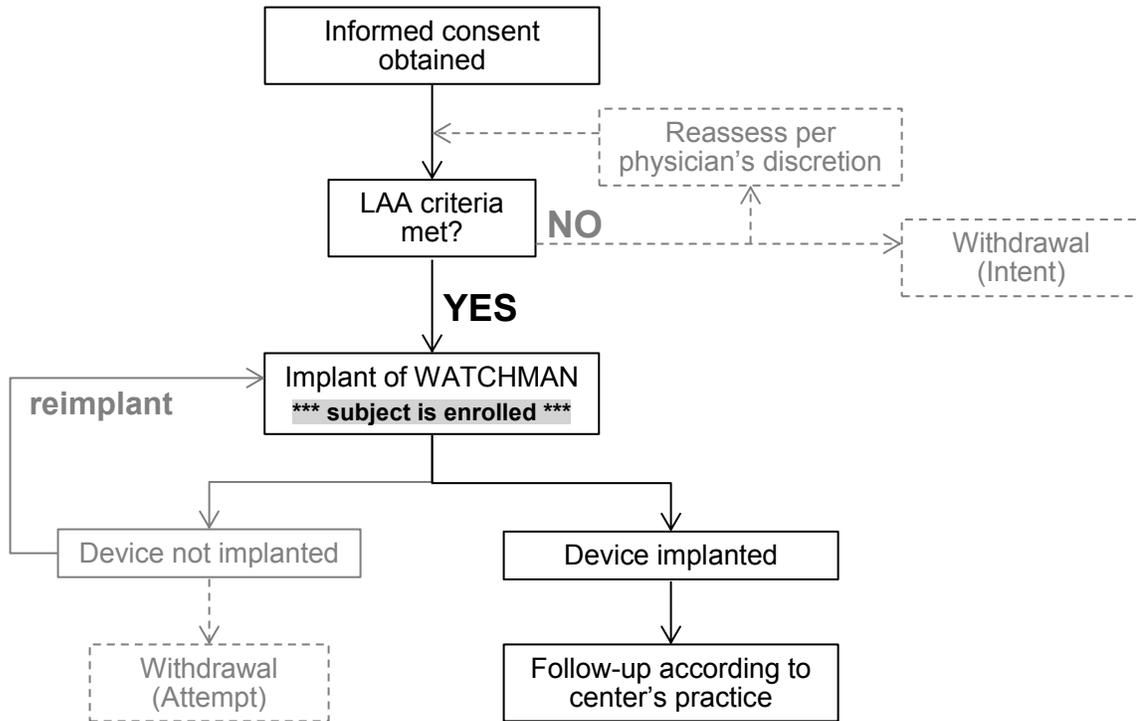
The date at which the patient status form has been completed will be the point of subject withdrawal.

### **Implant**

A subject who is successfully implanted with the WATCHMAN 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.

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 two years after implant according to the schedule and standard practice at the enrolling centers. There will be no additional visits, nor procedures, for subjects who participate in the study. Subjects are expected to be followed at implant, then at one post-implant visit (typically between 1-3 months of implant), and then annually through 2 years post implant. An intermediate visit may be a scheduled in a number of patients, per physician discretion. In order to reliably capture

patient status at study end a FU window of  $24 \pm 3$  months will be considered acceptable for scheduling the last visit.

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 in-office visit for at least the first annual visit.

**Table 2** provides an overview of the data to be collected at each visit.

**Table 2: Data Collection Overview**

Data Collected	BASELINE	IMPLANT	Follow Up		
			Post-implant Visit*	FU office visit	FU phone visit
Informed Consent	X				
Inclusion/Exclusion	X				
Demographic data	X				
Medical History	X				
LAA imaging (e.g. TEE)		X	X <sup>§</sup>	X <sup>**</sup>	
Medication Regimen	X	X	X	X	X
Current status and Vital Signs	X	X	X	X	
<i>Adverse Event Reporting</i>	<i>X</i>	<i>X</i>	<i>X</i>	<i>X</i>	<i>X</i>

\*expected 1-3 month from implant depending on center's practice

§ Control TEE/CT is clinical standard after the Watchman procedure to ensure sealing and exclude thrombus on the device prior to stop dual platelet inhibition or warfarin

\*\* collected only if performed, according to center's practice

### 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. Study Candidate Baseline

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 Baseline includes:

- Demographic data, including: age at time of consent, gender;
- Risk factors, including those used to calculate HAS-BLED, CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-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, if applicable.

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

Prior to implantation with the WATCHMAN device, an implant TEE (or alternative imaging method) is a clinical standard to confirm there is no thrombus in the LAA or left atrium. 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 first control LAA imaging, normally between 1-3 months post-implant, is a clinical standard after the WATCHMAN procedure, it is conducted to assess flow through and around the WATCHMAN 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 TEEs 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.

#### **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 LAA Closure Device should only be performed by physicians trained in percutaneous and transseptal procedures who have completed the WATCHMAN training program. Refer to the WATCHMAN LAA Closure Technology

Directions for Use for detailed instructions regarding the implantation and use of the WATCHMAN technology. The following will be assessed during implant procedure and documented on case report forms for enrolled subjects:

- WATCHMAN Device and Access System usage information, including device size and compression post-implant;
- 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 and adverse events 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 one post-implant visit (typically between 1-3 months of implant), and then annually through 2 years post implant or until the study is terminated. An intermediate visit may be scheduled in a number of patients, per physician discretion. In order to reliably capture patient status at study end a FU window of  $24 \pm 3$  months will be considered acceptable for scheduling the last visit. 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 annual 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 and adverse events 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 implant related clinical events (stroke/TIA (ischemic/non-ischemic), systemic embolism, major and minor bleeding)
  - Hospitalization (ICU and Ward) due to WATCHMAN implant related clinical events (stroke/TIA (ischemic/non-ischemic), systemic embolism, major and minor bleeding)
  - Specialist visits due to WATCHMAN implant related clinical events (stroke/TIA (ischemic/non-ischemic), systemic embolism, major and minor bleeding)
  - Diagnostic procedure following a clinical event related to WATCHMAN (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 and adverse events 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 implant related clinical events (stroke/TIA (ischemic/non-ischemic), systemic embolism, major and minor bleeding)
  - Hospitalization (ICU and Ward) due to WATCHMAN implant related clinical events (stroke/TIA (ischemic/non-ischemic), systemic embolism, major and minor bleeding)
  - Specialist visits due to WATCHMAN implant related clinical events (stroke/TIA (ischemic/non-ischemic), systemic embolism, major and minor bleeding)

- Diagnostic procedure following a clinical event related to WATCHMAN (stroke/TIA (ischemic/non-ischemic), systemic embolism, major and minor bleeding)

### 11.7. Study Completion

Each subject will be followed for 2 years after the implant. In order to reliably capture subject status at study end, FU assessment at  $24 \pm 3$  months following implant will be considered acceptable. 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, multi-center non-randomized observational study with no formal pre-specified hypothesis test. All subjects will be followed for up to 2 years or until the study is terminated.

A sample size of up to 1000 subjects was chosen to assess incidence of rare events with a large degree of precision. **Table 3** provides the two-sided 95% confidence interval width assuming an event rate of 5%.

**Table 3: Two-Sided Confidence Interval by Sample Size**

Sample Size	95% CI
500	5% $\pm$ 1.9%
750	5% $\pm$ 1.6%
1000	5% $\pm$ 1.4%

### 12.2. Statistical Analysis

Analysis will include all subjects enrolled into the study who undergo an attempted implant of the WATCHMAN device. While no formal hypothesis tests will be performed, descriptive statistics will be generated for the data collected at baseline, 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. Analyses may include, but will not be limited to, the following: procedural success, procedural complications, and incidence stroke/TIA.

A variety of methods may be utilized in order to assess associations between the likelihood of each of the three outcomes 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 4: Covariates of Interest.

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

- Univariate analysis of individual predictors, and subsequent construction of multivariate logistic regression models incorporating all significant univariate predictors.
- Parsimonious multivariate logistic regression models constructed through stepwise selection algorithm.
- Classification and regression tree models.

**Table 4: Covariates of Interest**

• Age $\geq$ 80 years
• Gender
• Type of AF (paroxysmal; persistent; permanent)
• Previous Stroke/TIA
• Previous major bleeding event
• HASBLED $\geq$ 3
• CHADS <sub>2</sub> $\geq$ 3

• CHA <sub>2</sub> DS <sub>2</sub> -VASc $\geq$ 5
• Type of anticoagulation therapy (Warfarin; NOACs; antiplatelet)
• 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 SAEs and device deficiencies that could have led to a SADE.
- Report to the IRB/EC and regulatory authorities any SAEs and device deficiencies that could have led to a SADE, if required by the national regulations or this protocol or by the IRB/EC, and supply BSC with any additional requested information related to the safety reporting of a particular event.
- 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/country 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, visits or risks as compared to patients who are routinely implanted with the WATCHMAN 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 Implant & Procedure**

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

1. • Air Embolism
2. • Allergic Reaction to Contrast Media/Meds
3. • Anemia Requiring Transfusion
1. • Arrhythmias
  - AV Fistula
2. • Bruising - Hematoma
1. • Cranial Bleed
  - Death
    1. • Device Embolization
    2. • Device Thrombus
  - Excessive Bleeding
  - Gastrointestinal Bleeding
3. • Groin Puncture Bleed
1. • Hypotension
1. • Inability to Move or Retrieve Device
2. • Infection/Pneumonia
1. ☐ Major Bleed Requiring Transfusion
2. • Pericardial Effusion
1. • Pleural Effusion
  - Post Procedure Anesthesia Effects
  - Pseudoaneurysm
2. • Pulmonary Edema
  - Stroke - Hemorrhagic
1. • Stroke - Ischemic
  - Systemic Embolism
2. • TEE Complications (throat pain, bleeding)
  - Thrombosis
  - Thrombus at Septal Puncture
3. • Transient Ischemic Attack (TIA)
  - Vasovagal Reactions

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 and not enrolled in this study. However, results from the data collected during this study may improve the management of WATCHMAN 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 device is its expected ability to prevent thromboembolic events originating in the LAA. The WATCHMAN 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 5.

**Table 5: Adverse Event Definitions**

Term	Definition
Adverse Event (AE)  <i>Ref: ISO 14155-2011</i>  <i>Ref: MEDDEV 2.7/3 12/2010</i>	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)  <i>Ref: ISO 14155-2011</i>  <i>Ref: MEDDEV 2.7/3 12/2010</i>	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)  <i>Ref: ISO 14155-2011</i>  <i>Ref: MEDDEV 2.7/3 12/2010</i>	Adverse event that: <ul style="list-style-type: none"> <li>○ Led to death,</li> <li>○ Led to serious deterioration in the health of the subject, that either resulted in:               <ul style="list-style-type: none"> <li>○ a life-threatening illness or injury, or</li> <li>○ a permanent impairment of a body structure or a body function, or</li> <li>○ in-patient or prolonged hospitalization of existing hospitalization, or</li> <li>○ medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function                   <ul style="list-style-type: none"> <li>○ Led to fetal distress, fetal death, or a congenital abnormality or birth defect.</li> </ul> </li> </ul> </li> </ul> <b>NOTE 1:</b> 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)  <i>Ref: ISO 14155-2011</i>  <i>Ref: MEDDEV 2.7/3 12/2010</i>	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

**Table 5: Adverse Event Definitions**

<b>Term</b>	<b>Definition</b>
Unanticipated Serious Adverse Device Effect (USADE)  <i>Ref: ISO 14155-2011</i>  <i>Ref: MEDDEV 2.7/3 12/2010</i>	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  <b>NOTE 1:</b> 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  <i>Ref: ISO 14155-2011</i>  <i>Ref: MEDDEV 2.7/3 12/2010</i>	A device deficiency is any inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.  <b>NOTE 1:</b> Device deficiencies include malfunctions, misuse or use errors, and inadequate labeling.

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

### **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 5 for AE definitions).

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:

4. The WATCHMAN device;
5. The WATCHMAN implant procedure;
6. 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);
7. Any WATCHMAN related procedures (i.e., clinical complications from TEE or other procedure required by labeling)

The following adverse events will also be reported:

8. Neurological events including, but not limited to, stroke, TIA or seizure which are not pre-study conditions
9. Any events possibly related to stroke/TIA, systemic embolization, death, etc.

## 10. Thrombosis

## 11. Bleeding complications requiring intervention or transfusion of blood.

Please refer to Appendix A 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 6:

**Table 6: Investigator Reporting Requirements**

Event Classification	Communication Method	Communication Timeline
Unanticipated Serious Adverse Device Effect	Complete AE eCRF page with all available new and updated information	<ul style="list-style-type: none"> <li>○ Within 1 business day of first becoming aware of the event.</li> <li>○ Terminating at the end of the study</li> </ul>
Serious Adverse Event including Serious Adverse Device Effects	Complete AE eCRF page with all available new and updated information	<ul style="list-style-type: none"> <li>○ Within 2 business days of first becoming aware of the event or as per local/regional regulations.</li> <li>○ Reporting required through the end of the study</li> </ul>
	Provide all relevant source documentation (unidentified) for reported event	<ul style="list-style-type: none"> <li>○ When documentation is available</li> </ul>
Adverse Event	Complete AE eCRF page, which contains such information as date of AE, treatment of AE resolution, assessment of seriousness and relationship to the device	<ul style="list-style-type: none"> <li>○ No later than 14 working days after becoming aware of the information</li> <li>○ Reporting required through the last visit of the patient in the study, with the exception of following up open adverse events until resolved or considered stable.</li> </ul>
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	Complete applicable Device Deficiency CRF page with all available new and updated information	<ul style="list-style-type: none"> <li>○ Investigators should report within 14 business days of first becoming aware of the event and as per local/regional regulations</li> <li>○ Reporting required through the end of the study</li> </ul>

**Table 6: Investigator Reporting Requirements**

<b>Event Classification</b>	<b>Communication Method</b>	<b>Communication Timeline</b>
less fortunate is considered a reportable event.		

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 14 business days 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 adverse event information to all participating investigators and regulatory authorities, as applicable. The Principal Investigator is responsible for informing the IRB/EC, and regulatory authorities of UADE and SAE as per local/regional requirements.

## **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

### ***21.2. Executive/Steering Committee***

An Executive Committee composed of the sponsor's Clinical Management and the study Coordinating Principal Investigator(s) may be convened. Responsibilities may include oversight of the overall conduct of the study with regard to protocol development, study

progress, subject safety, overall data quality and integrity, and first line review and final decision making of independent medical reviewer recommendations, as well as disseminating any study results through appropriate scientific sessions and publications. Executive Committee members may participate in the review and approval of all requests for data analysis, abstract and manuscript preparation, and submission. As appropriate, the Executive Committee may request participation of WATCHMAN Registry Investigators on the Committee.

## **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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## Appendix A - Definitions

### *A.1 Stroke/TIA definitions*

#### Broad definitions:

***Transient ischemic attack:*** An episode of acute neurological dysfunction presumed to be caused by transient ischemia, with rapid symptom resolution (usually 1–2 h), resolving completely within 24 hours. Neuroimaging without tissue injury.

***Stroke:*** An episode of acute neurological dysfunction presumed to be caused by ischemia or hemorrhage, persisting  $\geq 24$  hours or until death; preferably with positive neuroimaging study;

#### 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  $\geq 24$  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 tumour, 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)

(from From Leon MB, Eur Heart J. 2011 Jan;32(2):205-17)

### *A.2 Classification of Bleeding events*

In response to the need to develop, disseminate, and ultimately adopt standardized bleeding end-point definitions for patients 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 patient 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 patient 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:

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

**Type 3:****Type 3a:**

1. Overt bleeding plus hemoglobin drop of 3 to < 5 g/dL\* (provided hemoglobin drop is related to bleed)
2. Any transfusion with overt bleeding

**Type 3b:**

1. Overt bleeding plus hemoglobin drop  $\geq 5$  g/dL\* (provided hemoglobin drop is related to bleed),
2. Cardiac tamponade,
3. Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/haemorrhoid),
4. Bleeding requiring intravenous vasoactive agents

**Type 3c:**

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

**Type 4:**

1. CABG-related bleeding,
2. Perioperative intracranial bleeding within 48 h,
3. Reoperation after closure of sternotomy for the purpose of controlling bleeding
4. Transfusion of  $\geq 5$  U whole blood or packed red blood cells within a 48-h period,
5. 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)