Continued Access to PREVAIL (CAP2)
Clinical Protocol

IDE #G020312

Sponsored By

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Current Version: December 12, 2012

Revision History

Revision Number	Release Date	Section	Change	Reason for Change
AA	June 25, 2012	N/A	Migrating Atritech CAP2 Protocol into BSC Template	Alignment with BSC Clinical System SOPs
AB	July 2, 2012	11.6	Update to active clotting time (ACT)	To match ACT with that included in the clinical Directions for Use (DFU)
AC	July 18, 2012	Section 2 and 9.3	Clarification to the Exclusion Criteria	For clarification
AD	July 27, 2012	Section 5 and	Remove reference to	Obturator will not be

Revision History

Revision Number	Release Date	Section	Change	Reason for Change
		16	obturator	included in CAP2
AE	December 12, 2012	7 & 10	Clarify AE collection for screened failures	To address FDA requests
AF	TBD	11 & 21	Added NOAC caution and additional Stroke assessments	To address DSMB feedback

2. Protocol Synopsis

Continued Access to PREVAIL (CAP2)	
Objective(s)	To provide additional information about the safety and efficacy of the WATCHMAN LAA Closure Technology.
Marketing Performance Expectation	The WATCHMAN LAA Closure Technology is intended as an alternative to warfarin therapy for patients with non-valvular atrial fibrillation. 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 a prospective, non-randomized, multicenter study.
Planned Number of Subjects	Initial cohort of 300 subjects, up to a maximum of 1500 subjects.
Planned Number of Centers / Countries	60
Primary Endpoint	Descriptive statistics will be used for baseline, procedure and follow-up data collected through the study.
Follow-up Schedule	Subjects will be followed at intervals of 45 days, 6 months, 12 months, semi-annually through 3 years, and thereafter annually through 5 years post enrollment.
Study Duration	Subjects will be followed through 5 years post enrollment. It is anticipated that enrollment will be conducted over a period of two years.

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Required Medication Therapy	Warfarin, aspirin, clopidogrel, heparin, antibiotics, as applicable and outlined within the protocol
Key Inclusion Criteria	A subject may be enrolled in the study if all of the following inclusion criteria are met: 1. The subject is 18 years of age or older 2. The subject has documented paroxysmal, persistent, or permanent non-valvular atrial fibrillation (i.e., the subject has not been diagnosed with rheumatic mitral valvular heart disease) 3. The subject is eligible for long-term warfarin therapy 4. The subject has a calculated $CHADS_2$ score of 2 or greater; Subjects with a $CHADS_2$ score of 1 may be included if any of the following apply (according to the ACC/AHA/ESC 2006 Guidelines for the Management of Subjects with Atrial Fibrillation subjects requiring warfarin therapy) : • The subject is a female age 75 or older • The subject has a baseline Left Ventricular Ejection Fraction (LVEF) $\geq$ 30% and < 35% • The subject is age 65-74 and has diabetes or coronary artery disease • The subject is age 65 or greater and has documented congestive heart failure 5. The subject or legal representative is able to understand and willing to provide written informed consent to participate in the trial 6. The subject is able and willing to return for required follow-up visits and examinations
Key Exclusion Criteria	Subjects will be excluded from the study if they meet any of the following criteria: 1. The subject requires long-term warfarin therapy (i.e., even if the device is implanted, the subjects would not be eligible to discontinue warfarin due to other medical conditions requiring chronic warfarin therapy). Additionally, a subject with any of the following is excluded: • Thrombosis occurring at a young age (<40 years old)

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	• Idiopathic or recurrent venous thromboembolism • Thrombosis at an unusual site (i.e., cerebral veins, hepatic veins, renal veins, inferior vena cava, mesenteric veins) • Family history of venous thromboembolism or of inherited prothrombotic disorder • Recurrence or extension of thrombosis while adequately anticoagulated 2. The subject is contraindicated for warfarin therapy or cannot tolerate long-term warfarin therapy 3. The subject is contraindicated or allergic to aspirin 4. The subject is indicated for antiplatelet therapy other than aspirin (for example, a subject indicated for clopidogrel, prasugrel, ticlopidine or ticagrelor due to DES is excluded from enrollment during the dosing regimen). A subject completing a course of antiplatelet therapy may be enrolled after a 7 day washout period 5. The subject had any interventional or surgical procedure within 30 days prior to enrollment or is planning to have an interventional or surgical procedure in the time between the WATCHMAN device implant and 45-day TEE (e.g., cardioversion, ablation, cataract surgery, dental surgery) 6. The subject had a prior stroke or TIA within the 90 days prior to enrollment 7. The subject has had an MI within 90 days prior to enrollment 8. The subject has a history of atrial septal repair or has an ASD/PFO device 9. The subject has an implanted mechanical valve prosthesis 10. The subject suffers from New York Heart Association Class IV Congestive Heart Failure at the time of enrollment 11. The subject has symptomatic carotid disease (defined as >50% stenosis with symptoms of ipsilateral transient or visual TIA evidenced by amaurosis fugax, ipsilateral hemispheric TIAs or ipsilateral stroke); if subject has a history of carotid stent or endarterectomy the subject is eligible if there is < 50% stenosis 12. The subject's AF is defined by a single occurrence of AF

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	13. The subject had a transient case of AF (i.e., secondary to CABG, interventional procedure, etc.) 14. The subject's left atrial appendage is obliterated 15. The subject has undergone heart transplantation 16. The subject is currently treated with antibiotics for an active infection 17. The subject has a resting heart rate > 110 bpm 18. The subject has thrombocytopenia (defined as < 70,000 platelets/mm^3) or anemia with hemoglobin concentration of < 10 g/dl (i.e., anemia as determined by the investigator which would require transfusion) 19. The subject is actively enrolled in a concurrent clinical study of an investigational drug or investigational device (study specifics may be reviewed with the sponsor prior to enrollment to confirm a concurrent study will not interfere with the outcomes of this study) 20. The subject participated in any of the following studies: PROTECT AF, CAP Registry, or PREVAIL. If the subject received a subject ID number for a prior WATCHMAN study, the subject may not be enrolled. PROTECT AF control subjects may be considered for participation if they have completed 5 year follow up 21. The subject is pregnant or pregnancy is planned during the course of the investigation 22. The subject has a life expectancy of less than two years 23. The subject is unable to complete follow-up visits for the duration of the study *Echo Exclusion Criteria* A subject is excluded from the study if any of the following echocardiographic exclusion criteria (as assessed via TTE and TEE) are met: 1. The subject has LVEF < 30% 2. The subject has intracardiac thrombus or dense spontaneous echo contrast as visualized by TEE and determined by the echocardiographer within 2 days prior to implant 3. The subject has an existing pericardial effusion > 2mm

<table>
<tr><th colspan="2">Continued Access to PREVAIL (CAP2)</th></tr>
<tr><td></td><td>4. The subject has a high risk patent foramen ovale (PFO) with an atrial septal aneurysm excursion > 15mm or length ≥ 15mm
5. The subject has a high risk PFO with a large shunt defined as early, within 3 beats or substantial passage of bubbles
6. The subject has significant mitral valve stenosis (i.e., MV <1.5 cm^2)
7. The subject has complex atheroma with mobile plaque of the descending aorta or aortic arch
8. The subject has a cardiac tumor</td></tr>
<tr><td colspan="2">Statistical Methods</td></tr>
<tr><td>Primary Statistical Hypothesis</td><td>Descriptive statistics will be used for baseline, procedure and follow-up data collected through the study. Analyses may include, but will not be limited to, the following: procedural success, procedural complications, and incidence of stroke leading to significant disability/death</td></tr>
<tr><td>Statistical Test Method</td><td>No formal pre-specified hypotheses will be tested.</td></tr>
<tr><td>Sample Size Parameters</td><td>A sample size of up to 1500 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 width assuming an event rate of 5%.
<table>
<tr><th>Sample Size</th><th>95% CI Width</th></tr>
<tr><td>1000</td><td>2.8%</td></tr>
<tr><td>1250</td><td>2.5%</td></tr>
<tr><td>1500</td><td>2.3%</td></tr>
</table></td></tr>
</table>

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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.[1] 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.[3,4,5] 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 times it is found this drug is not well tolerated.

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 been investigating the use of a permanent implantable device to seal off the left atrial appendage, the location where the vast majority of thrombi originates in AF patients. This device may provide an alternative to warfarin therapy in non-valvular AF patients who require thromboembolic protection.

ii) WATCHMAN Therapy

The WATCHMAN® Left Atrial Appendage Closure Technology is intended for patients with non-valvular atrial fibrillation who require treatment for potential thrombus formation and are eligible for warfarin therapy.

The implanted component of the system, hereafter referred to as the WATCHMAN device, is a novel device designed to prevent the embolization of thrombi that may form in the left atrial appendage (LAA). The WATCHMAN device may prevent the occurrence of ischemic stroke and systemic thromboembolism in patients with non-valvular atrial fibrillation (AF) who require treatment for potential thrombus formation. It may also reduce the risk of life-threatening bleeding events such as hemorrhagic stroke as seen in patients on warfarin therapy. The WATCHMAN is manufactured by Atritech, a subsidiary of 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 4-1** lists the clinical studies conducted in the U.S. with the WATCHMAN device. The pivotal study, 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. The Pre-Market Application (PMA) was therefore submitted to FDA in August 2008. The FDA requested that a second pivotal study be conducted to confirm the results of the PROTECT AF study. The second pivotal study, PREVAIL, was conducted to provide additional information on the implant procedure and complication rates associated with the device. When available, the results from the PREVAIL study will be submitted to FDA in a Pre-Market Application for consideration of commercial approval of the WATCHMAN device in the U.S. This continued access study will permit availability of the device to investigators and subjects during the preparation and FDA review of the Pre-Market Application.

Table 4-1 U.S. 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 ongoing
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
PREVAIL (pivotal study)	Nov 2010 – Ongoing at time of protocol development	Up to 475	Up to 50	Ongoing through 5 years

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 trans-septal technique under fluoroscopic and echocardiographic guidance.

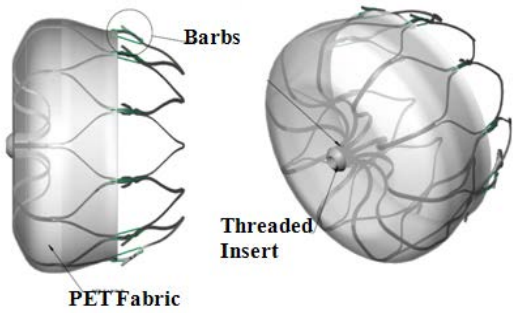
The WATCHMAN LAA Closure Technology is a three-component system which includes the WATCHMAN LAA Closure Device (WATCHMAN device), the WATCHMAN Delivery System and the WATCHMAN Access Sheath.

i) WATCHMAN Device

The WATCHMAN device is comprised of a self-expanding nitinol frame structure with fixation barbs around the device perimeter and a permeable polyester fabric that covers the atrial facing surface of the device (**Figure 5-1**). 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 5-1 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 12F.

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 14F 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

This Continued Access Protocol 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.

Subjects with non-valvular AF who require treatment for potential thrombus formation, and are eligible for warfarin therapy, will be screened to participate in the study. Subjects will be screened via review of medical history, transthoracic echocardiography (TTE) and TEE testing. Once study eligibility is determined, subjects will be enrolled and implanted with the

WATCHMAN device. After implant, subjects will receive warfarin therapy until TEE imaging has confirmed adequate sealing of the LAA. Successfully implanted subjects will be followed post enrollment for assessment of adverse events at intervals of 45 days, 6 months, 12 months, semi-annually through 3 years, and thereafter annually through 5 years.

7. Endpoint Analysis

Descriptive statistics will be used for baseline, procedure and follow-up data collected through the study. Analyses may include, but will not be limited to, the following: procedural success, procedural complications, and incidence of stroke leading to significant disability/death. Any adverse events associated with screened failures who have diagnostic testing to assess eligibility for the device or for device implantation, or who have medication changes in preparation for device implantation will be included in the analyses.

8. Design

This is a prospective, non-randomized, multicenter study to provide additional information about the safety and efficacy of the WATCHMAN LAA Closure Technology.

This study will be conducted at up to 60 investigational sites in the U.S. and enroll an initial cohort of up to 300 subjects. Incremental enrollment increases may be requested during the study to reach a maximum of 1500 subjects. FDA approval will be obtained prior to proceeding with the next cohort of subjects. Additionally, enrollment may terminate early if the device is approved for commercial use or when the PMA review is complete. The 60 sites will include those physicians with prior WATCHMAN experience demonstrated in the PREVAIL or PROTECT AF pivotal studies.

8.1. *Scale and Duration*

Subjects will be followed at intervals of 45 days, 6 months, 12 months, semi-annually through 3 years, and thereafter annually through 5 years post enrollment.

It is anticipated that enrollment will be conducted over a period of two years.

8.2. *Implant Procedure Training*

Investigators in the study will be those exhibiting proficiency in the trans-septal approach into the left atrium. Investigators with prior WATCHMAN implant experience in the PROTECT AF or PREVAIL studies will not be required to repeat operator training for this continued access study.

New operators must complete the WATCHMAN training program. Operator training includes the following elements:

- On-line pre-study examination
- Interactive on-line WATCHMAN case studies
- Case observations with an experienced WATCHMAN implanting physician

- Hands-on training for implanting physicians and lab staff on the WATCHMAN implant procedure from preparation to implantation and follow-up

8.3. *Treatment Assignment*

Not Applicable

8.4. *Justification for the Study Design*

Clinical evaluation of the WATCHMAN LAA Closure Technology has been ongoing since 2002, with all U.S. studies conducted under IDE #G020312. The pivotal study, 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. The Pre-Market Application (PMA) was therefore submitted to FDA in August 2008. The FDA requested that a second pivotal study be conducted to confirm the results of the PROTECT AF study. The second pivotal study, PREVAIL, was conducted to provide additional information on the implant procedure and complication rates associated with the device. When available, the results from the PREVAIL study will be submitted to FDA in a Pre-Market Application for consideration of commercial approval of the WATCHMAN device in the U.S. This continued access study will permit availability of the device to investigators and subjects during the preparation and FDA review of the Pre-Market Application.

9. Subject Selection

9.1. *Study Population and Eligibility*

The eligibility criteria for this continued access study are the same as the PREVAIL pivotal study. All subjects who present with non-valvular AF and are eligible for warfarin therapy will be considered for inclusion into the study. Those subjects who fulfill the inclusion criteria, do not meet any of the exclusion criteria, and provide written consent will be invited to participate. Qualified subjects will undergo TTE and TEE testing to further determine eligibility for the study. Only subjects meeting all criteria will be enrolled.

$CHADS_2$ Eligibility Criteria

The $CHADS_2$ score will be calculated for potential subjects as a basis for inclusion into the study. Subjects with a $CHADS_2$ score of 2 or greater are permitted in the study as well as some subjects with a $CHADS_2$ score of 1 as described in the Inclusion Criteria. The $CHADS_2$ score is calculated using the following stroke risk factors:

- 1 point is assigned for documented congestive heart failure (defined as having recent heart failure-related symptoms, within the previous 100 days, and the presence of moderate or severe left ventricle systolic dysfunction on echocardiography)
- 1 point is assigned for documented hypertension (systolic > 160 mmHg or well-controlled by anti-hypertensive medication)

- 1 point is assigned for subject age of 75 years or older
- 1 point is assigned for diabetes
- 2 points are assigned for prior cerebral ischemic stroke or Transient Ischemic Attack (TIA)

9.2. *Inclusion Criteria*

A subject may be enrolled in the study if all of the following inclusion criteria are met:

1. The subject is 18 years of age or older
2. The subject has documented paroxysmal, persistent, or permanent non-valvular atrial fibrillation (i.e., the subject has not been diagnosed with rheumatic mitral valvular heart disease)
3. The subject is eligible for long-term warfarin therapy
4. The subject has a calculated $CHADS_2$ score of 2 or greater; Subjects with a $CHADS_2$ score of 1 may be included if any of the following apply (according to the ACC/AHA/ESC 2006 Guidelines for the Management of Subjects with Atrial Fibrillation subjects requiring warfarin therapy) :
   - The subject is a female age 75 or older
   - The subject has a baseline Left Ventricular Ejection Fraction (LVEF) $\geq$ 30% and < 35%
   - The subject is age 65-74 and has diabetes or coronary artery disease
   - The subject is age 65 or greater and has documented congestive heart failure
5. The subject or legal representative is able to understand and willing to provide written informed consent to participate in the trial
6. The subject is able and willing to return for required follow-up visits and examinations

9.3. *Exclusion Criteria*

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

1. The subject requires long-term warfarin therapy (i.e., even if the device is implanted, the subjects would not be eligible to discontinue warfarin due to other medical conditions requiring chronic warfarin therapy). Additionally, a subject with any of the following is excluded:
    - Thrombosis occurring at a young age (<40 years old)
    - Idiopathic or recurrent venous thromboembolism
    - Thrombosis at an unusual site (i.e., cerebral veins, hepatic veins, renal veins, inferior vena cava, mesenteric veins)
    - Family history of venous thromboembolism or of inherited prothrombotic disorder
    - Recurrence or extension of thrombosis while adequately anticoagulated
2. The subject is contraindicated for warfarin therapy or cannot tolerate long-term warfarin therapy
3. The subject is contraindicated or allergic to aspirin
4. The subject is indicated for antiplatelet therapy other than aspirin (for example, a subject indicated for clopidogrel, prasugrel, ticlopidine or ticagrelor due to DES is excluded from enrollment during the dosing regimen). A subject completing a course of antiplatelet therapy may be enrolled after a 7 day washout period
5. The subject had any interventional or surgical procedure within 30 days prior to enrollment or is planning to have an interventional or surgical procedure in the time between the WATCHMAN device implant and 45-day TEE (e.g., cardioversion, ablation, cataract surgery, dental surgery)
6. The subject had a prior stroke or TIA within the 90 days prior to enrollment
7. The subject has had an MI within 90 days prior to enrollment
8. The subject has a history of atrial septal repair or has an ASD/PFO device
9. The subject has an implanted mechanical valve prosthesis
10. The subject suffers from New York Heart Association Class IV Congestive Heart Failure at the time of enrollment
11. The subject has symptomatic carotid disease (defined as >50% stenosis with symptoms of ipsilateral transient or visual TIA evidenced by amaurosis fugax, ipsilateral hemispheric TIAs or ipsilateral stroke); if subject has a history of carotid stent or endarterectomy the subject is eligible if there is < 50% stenosis
12. The subject's AF is defined by a single occurrence of AF
13. The subject had a transient case of AF (i.e., secondary to CABG, interventional procedure, etc.)
14. The subject's left atrial appendage is obliterated
15. The subject has undergone heart transplantation
16. The subject is currently treated with antibiotics for an active infection
17. The subject has a resting heart rate > 110 bpm
18. The subject has thrombocytopenia (defined as < 70,000 platelets/mm^3) or anemia with hemoglobin concentration of < 10 g/dl (i.e., anemia as determined by the investigator which would require transfusion)

19. The subject is actively enrolled in a concurrent clinical study of an investigational drug or investigational device (study specifics may be reviewed with the sponsor prior to enrollment to confirm a concurrent study will not interfere with the outcomes of this study)
20. The subject participated in any of the following studies: PROTECT AF, CAP Registry, or PREVAIL. If the subject received a subject ID number for a prior WATCHMAN study, the subject may not be enrolled. PROTECT AF control subjects may be considered for participation if they have completed 5 year follow up
21. The subject is pregnant or pregnancy is planned during the course of the investigation
22. The subject has a life expectancy of less than two years
23. The subject is unable to complete follow-up visits for the duration of the study

Echo Exclusion Criteria

A subject is excluded from the study if any of the following echocardiographic exclusion criteria (as assessed via TTE and TEE) are met:

1. The subject has LVEF < 30%
2. The subject has intracardiac thrombus or dense spontaneous echo contrast as visualized by TEE and determined by the echocardiographer within 2 days prior to implant
3. The subject has an existing pericardial effusion > 2mm
4. The subject has a high risk patent foramen ovale (PFO) with an atrial septal aneurysm excursion > 15mm or length $\geq$ 15mm
5. The subject has a high risk PFO with a large shunt defined as early, within 3 beats or substantial passage of bubbles
6. The subject has significant mitral valve stenosis (i.e., MV <1.5 cm^2)
7. The subject has complex atheroma with mobile plaque of the descending aorta or aortic arch
8. The subject has a cardiac tumor

10. Subject Accountability

10.1. *Enrollment*

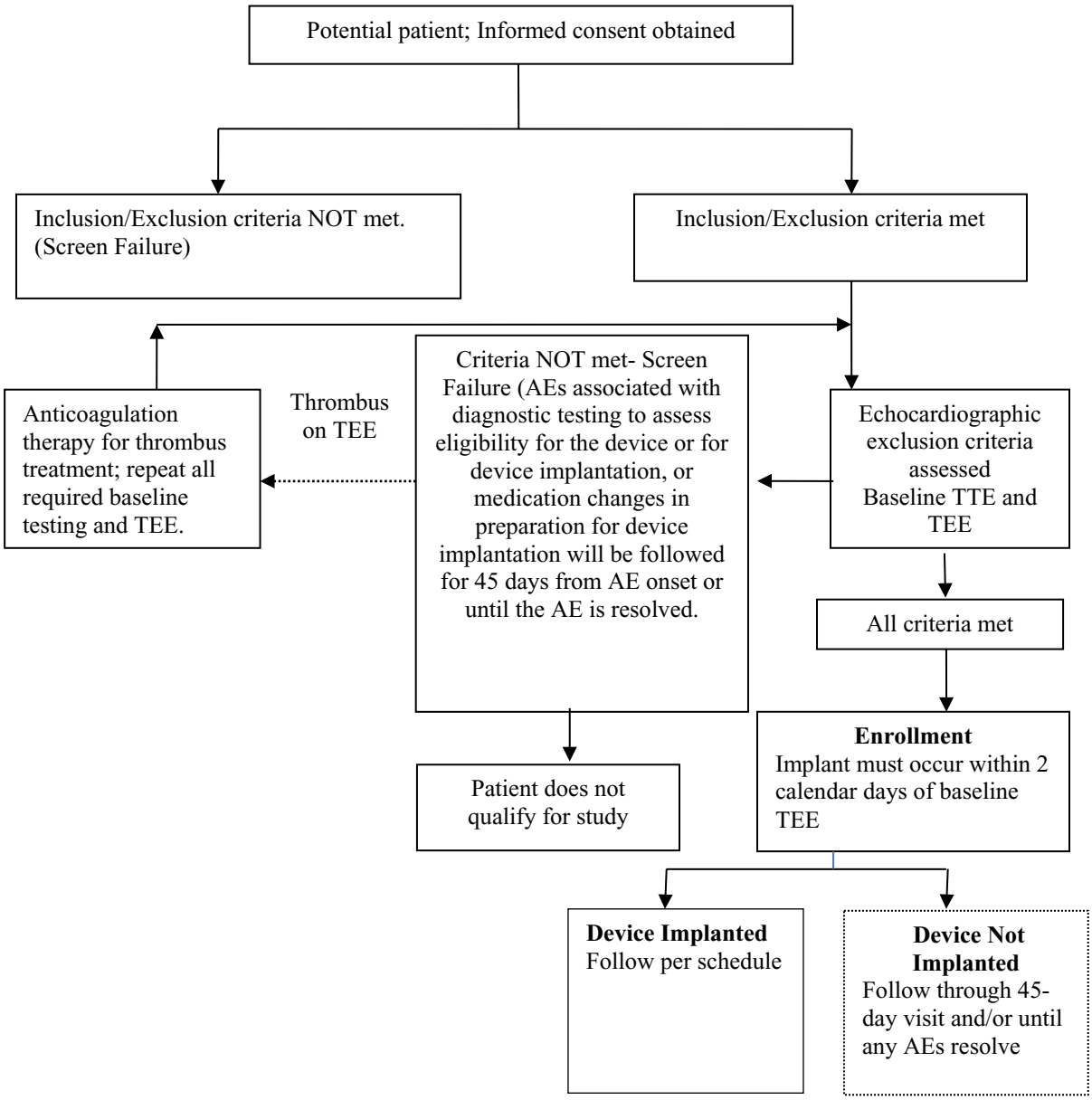
All adult subjects with non-valvular AF who require treatment for potential thrombus formation and are eligible for warfarin therapy shall initially be screened as candidates for the study. Subjects receiving dabigatran or rivaroxaban prior to enrollment may be considered for inclusion in the study however they will be required to be treated with warfarin post-WATCHMAN implant. Those subjects who provide consent and meet the Inclusion and Clinical Exclusion Criteria will undergo an echocardiographic examination (TTE and TEE) to further evaluate Echo Exclusion Criteria.

If the baseline TEE confirms the presence of any intracardiac thrombus, the subject cannot be enrolled in the study. The subject may be treated with anticoagulation therapy and, after an appropriate period of time, return for another baseline TEE to assess evidence of intracardiac

thrombus and other baseline criteria. Only when the thrombus has completely resolved is the subject eligible for study enrollment.

Once a subject meets all of the entrance criteria he/she is considered enrolled at the time of venous access for the implant procedure and must be implanted within 2 calendar days of the baseline TEE.

Figure 10.1-2 Subject Enrollment Overview



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 risks and should only be enrolled if willing to fully participate in the study. In the event a subject does decide to withdraw from the study, every effort should be made to obtain full information on any ongoing adverse events. Subjects will be given the following withdrawal options:

1) Telephone contact to complete some or all of the visit requirements that can be completed over the phone including adverse event reporting
2) Telephone contact for adverse event reporting only
3) No contact

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.

Subjects with unsuccessful implant attempts should be followed through the 45-day visit for any adverse events or followed through the resolution of existing adverse events, whichever is later, and then be withdrawn from the study.

Subject withdrawal and lost to follow-up will be documented on the End of Study case report form.

10.3. *Subject Status and Classification*

- Consent Ineligible/Screen Failure: A subject who has signed the informed consent but is found to not meet the eligibility criteria, and does not undergo an implant.
- Unsuccessful Implant Attempt: A subject who meets all the eligibility criteria, is considered enrolled at the time of venous access at the beginning of an implant attempt but does not receive an implant. If the device is not successfully implanted, the post procedure medication regimen will be administered per physician discretion. The subject will be followed in the study through the 45-day follow-up visit or through resolution of any peri-procedural adverse events, whichever is later.
- Implant: A subject who receives an implant.

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 and completely 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 are to be submitted to the sponsor within two weeks of completion of a study visit.

11.2. *Stroke Assessments*

Three stroke assessment scales will be routinely collected at baseline and follow-up visits for all subjects. These scales include the following:

- National Institutes of Health Stroke Scale (NIHSS): The NIHSS is an assessment tool which quantifies stroke related neurological deficit. This assessment must be conducted in person to provide valuable information on stroke severity. This test will be performed at baseline and at all office visits. It must be conducted by a neurologist or personnel who have a current certification to conduct the NIHSS.
- Modified Rankin Scale (MRS): This scale assesses the severity of stroke disability and functional dependence of subjects. This test will be collected at baseline and all office and telephone follow-up visits. The assessment must be performed by either a neurologist or personnel who have completed a certification for the MRS.
- Barthel Index: The Barthel Index quantifies a subject's ability to perform typical daily functions. This test will be collected at baseline and all office and telephone follow-up visits.

11.3. *Imaging Requirements*

All subjects will undergo a baseline TEE and TTE and follow-up TEE at the 45-day visit and 12 month visits. All study required TEEs will be performed in accordance with the Imaging Manual.

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

i) Transthoracic Echocardiogram (TTE)

All TTEs will be conducted according to the Imaging Manual. The baseline TTE will be done to evaluate LVEF to confirm subject eligibility. An LVEF value obtained from a TTE performed within 60 days prior to enrollment may be used. If a significant cardiac event occurs after the TTE which causes a change in cardiac status [i.e., major Congestive Heart Failure (CHF) decompensation] the baseline TTE should be repeated prior to enrollment.

ii) Transesophageal Echocardiogram (TEE)

All TEEs will be conducted according to the Imaging Manual. The implant TEE will allow the investigator to obtain proper measurements of the LAA to correctly size the device,

confirm device release criteria are met prior to device release, and to confirm adverse events have not occurred during the implant procedure (i.e., pericardial effusion).

The 45-day and 12-month TEEs are conducted to assess flow through and around the WATCHMAN device and to verify there is no thrombus on the surface of the device. As required by protocol, some subjects may also have a 6-month TEE if the 45-day TEE demonstrates inadequate seal around the device.

Table 11.3-1 provides an overview of the data to be collected at each visit.

Table 11.3-1 Data Collection Overview

Evaluation	Screen	Implant	Post	Follow-Up				
				45 Day Visit	6 Month Visit	12 Month Visit	18 month 30 month Telephone	Annual Visits
Informed Consent	X							
Assess Inclusion/Exclusion	X							
Medical History	X							
Pregnancy Test[a]	X							
TTE	X							
TEE	X[b]	X		X	If no seal at 45-day	X		
Brain Imaging (CT/MRI) [d]	X[c]		As required[d]	As required[d]	As required[d]	As required[d]	As required[d]	As required[d]
Serum Creatinine, Platelet count, Hemoglobin	X							
Review Medication Regimen	X	X	X	X	X	X	X	X
Vital Signs	X			X		X		X
NIH Stroke Scale	X			X		X		X
Barthel Index / Modified Rankin	X			X	X	X	X	X
Adverse Event Monitoring	X	X	X	X	X	X	X	X

a For women of childbearing potential only
b Within 2 calendar days prior to enrollment
c Obtain at baseline if subject had prior stroke or TIA
d Brain MRI or CT required if subject suffers stroke or TIA
e Adverse events associated with diagnostic testing to assess eligibility for the device or for device implantation, and AEs associated with medication changes in preparation for device implantation will be collected.

11.4. *Study Candidate Baseline Screening*

After the subject informed consent document has been signed, subject eligibility will be determined through evaluation of the inclusion and exclusion criteria. Only those subjects who provide consent and meet all of the study entrance criteria will be enrolled. Enrollment is defined as the time of venous access at the beginning of an implant attempt.

Subjects who provide informed consent but do not meet all of the study entrance criteria or do not have an implant attempt will be considered screening failures.

The following will be assessed during baseline screening and documented on the baseline case report forms for enrolled subjects:

- Medical and cardiac history
- Current medical status, vital signs and AF status
- Pregnancy test for women of child-bearing potential
- Laboratory analysis (hemoglobin, platelet count, serum creatinine)
- Current medication regimen for the use of antiplatelet and anticoagulation medications
- Subjects with prior history of ischemic stroke, hemorrhagic stroke or TIA are required to have a Baseline MRI or CT obtained
- NIH Stroke Scale, Barthel Index, and Modified Rankin Scale
- TTE – If the subject had a TTE within 60 days prior to enrollment it will not need to be repeated as long as the subject did not have an appreciable difference in cardiac status since the TTE was performed.
- TEE – The TEE must be completed prior to enrollment to confirm eligibility criteria. As this is an invasive screening procedure, it is recommended the TEE be performed at the end of the screening process. Subjects will be implanted within 2 calendar days of the baseline TEE.

11.5. *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. Subjects must be informed about the investigational nature of the therapy and the potential benefits and risks of the WATCHMAN device prior to enrollment. Only those subjects (or legal guardians) who voluntarily provide written consent to participate will be allowed to continue in the screening process. A subject must receive informed consent and sign and date a current IRB approved consent document. Subjects should be informed that even if they agree to participate in the study, the baseline screening and TEE may demonstrate they are not candidates for the study. The original, signed document is to be kept with the subject's file and a copy must be provided to the subject.

11.6. *Implant Procedure*

i) Thrombus Assessment Prior to Implant

Prior to implantation with the WATCHMAN device, the peri-procedural TEE should confirm there is no thrombus in the LAA or left atrium. If thrombus is identified the subject may not be implanted and appropriate anticoagulation should be prescribed. If venous access was achieved at the time a thrombus is detected, the subject is considered enrolled. The subject may not be implanted, and will be considered an implant failure.

If thrombus is identified prior to the implant, but without venous access, the subject will be considered a screening failure and may be re-screened after the thrombus has resolved.

ii) Implant of the WATCHMAN Device

Investigators performing the WATCHMAN implant procedure will be chosen based on their familiarity with and training in currently accepted trans-septal and left heart techniques.

The decision to bridge prior to the procedure with warfarin and/or heparin will be at the discretion of the operator.

Antibiotics for subacute bacterial endocarditis prophylaxis are recommended for administration in a single dose before the procedure as outlined in the American Heart Association Guideline for Prevention of Infective Endocarditis. If the dosage of antibiotic is inadvertently not administered before the procedure, the dosage may be administered up to 2 hours after the procedure. Refer to the Guidelines for more details (Circulation 2007;116;1736-1754 or current update).

Subjects should be fully heparinized, per hospital policy, throughout the procedure with a recommended active clotting time (ACT) of 200 - 250 seconds. An ACT should be obtained at least every 30 minutes throughout the procedure, or per standard practice at each investigative center, to ensure an appropriate ACT is maintained for the duration of the procedure.

TEE imaging and fluoroscopy are required during the WATCHMAN implant procedure to assist the investigator to appropriately guide the WATCHMAN Access System into the LAA, obtain proper measurements of the LAA to correctly size the device, and to ensure that the device meets implant release criteria. Intraoperative TEE imaging should be performed in accordance with the Imaging Manual for the collection of images. TEE imaging will include at least one measurement of the maximum LAA ostium width and maximum appendage length to confirm measurements obtained during the baseline TEE as well as to ensure all post device release criteria are met during the procedure and captured on imaging.

Implanting physicians need to be cautious of inadvertently introducing air entrapped within the Access Sheath. The operator must be diligent in properly flushing the sheath to prevent air from becoming entrapped within the sheath and then embolizing into the systemic circulation.

Reference WATCHMAN LAA Closure Technology Instructions for Use (IFU) for complete information on the implant procedure and appropriate device release criteria.

iii) Prior to Device Release

To ensure implant release criteria have been satisfied according to the IFU for position, size, stability and seal complete the following:

- Using both fluoroscopy and TEE, confirm the implant is appropriately positioned at or slightly distal to and spans the entire LAA opening (perform multiple contrast injections at multiple viewing angles).
- Confirm appropriate implant size by measuring the deployed diameter of the implant *in situ* using fluoroscopy and/or TEE to ensure appropriate device compression guidelines are met.
- Confirm acceptable implant stability by performing a gentle tug on the device deployment knob to ensure the implant is well anchored within the LAA.
- Confirm via fluoroscopy and TEE that all lobes are covered by the device.

iv) Unsuccessful Implant Attempt

If the WATCHMAN device is not successfully implanted, the post procedure medication regimen (See **Table 11.7-1**) will be administered per physician discretion. The subject will be followed in the study through the 45-day follow-up visit or through resolution of any peri-procedural adverse events, whichever is later. The TEE evaluation and in-office visit are not necessary at the 45-day visit for subjects without a device; these subjects may have a 45-day telephone follow-up in lieu of an office visit. After completion of the 45-day visit and resolution of adverse events, the subject will be exited from the study.

11.7. *Medication Regimen for the Study*

i) Discharge Through 45-Day TEE

Following device placement warfarin therapy should be appropriately adjusted so as to achieve a therapeutic INR of 2.0 – 3.0. Implanted subjects are to be on adjusted dose warfarin therapy through at least the 45-day follow-up TEE. While on warfarin therapy, subjects will also be prescribed 81mg aspirin. Aspirin is necessary post device placement to mitigate platelet aggregation. Subjects will remain on warfarin until the 45-day TEE evaluation has shown adequate seal of the LAA.

ii) 45-Day TEE

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

- If the 45-day TEE shows adequate seal of the LAA with a jet around the device $\leq$ 5mm,
    - Warfarin therapy will be discontinued,

- Aspirin dosage will be increased to 325mg indefinitely,
- Clopidogrel will be initiated and taken until the 6 month follow-up visit then discontinued, and
- There will not be a TEE at the 6 month visit

- If the 45-day TEE shows inadequate seal of residual LAA blood flow with a jet size > 5mm around the margins of device,
  - The subject will remain on warfarin therapy and a 6 month TEE will be required to assess LAA seal,
  - Aspirin dosage will remain 81mg while the subject is on warfarin therapy, and
  - Clopidogrel will not be initiated

iii) 6 Month Visit

A 6 month TEE is only required for those subjects determined to have an inadequate seal at the 45-day TEE.

- If the 6 month TEE shows adequate seal of the LAA with a jet around the device ≤ 5mm,
  - Warfarin therapy will be discontinued, and
  - Aspirin dosage will be increased to 325mg indefinitely
- If the 6 month TEE shows inadequate seal of residual LAA blood flow with a jet size > 5mm around the margins of device,
  - The subject will remain on warfarin therapy until a TEE can confirm adequate LAA seal, and
  - Aspirin dosage will remain 81mg while the subject is on warfarin therapy

Caution should be used if considering use of novel oral anticoagulants since this has not been studied in patients with a WATCHMAN device. If anticoagulation is required for any reason beyond what is specified in the protocol, ensure medication labeling is followed; specifically that related to the abrupt discontinuation of NOACs in patients with non-valvular atrial fibrillation without adequate continuous anticoagulation.

Table 11.7-1 Medication Regimen Post Implant

Visit Interval	Warfarin	Aspirin	Clopidogrel
Implant – 45-Day	Yes Adjusted dose to achieve INR of 2.0 – 3.0	Yes 81mg while on warfarin	No
LAA Seal per 45-Day TEE			
45-Day – 6-Month	**Stop** warfarin	Yes 325mg recommended	Yes, **Start** Clopidogrel
6-Month – 5 Year	No	Yes 325mg recommended	No, **Stop** Clopidogrel at 6 month visit
No LAA Seal per 45-day TEE			
45-Day – 6-Month	Yes	Yes 81mg while on warfarin	No
6-Month – 5 Year	Discontinue when LAA seal adequate	81mg for subjects while on warfarin If no warfarin therapy, then adult aspirin (325mg) indefinitely	No

11.8. *Follow-up Procedures*

Subjects will be followed at post-enrollment intervals of 45 days, 6 months, 12 months, semi-annually through 3 years, and thereafter annually through 5 years or until the study is terminated. A projected follow-up timeline will be provided to the site for each subject upon enrollment.

A Follow-Up Case Report Form will be completed for each office and telephone visit. **Table 11.8-1** provides the visit target visit dates and visit window ranges.

Table 11.8-1 Visit Windows

Follow-up visit	Target (days post-implant)	Range
45-Day	45 days	30-60 days
6-Month	182 days	152-242 days
12-Month	365 days	335-425 days
18-Month	547 days	517-607 days
24-Month	730 days	700-790 days
30-Month	913 days	883-973 days
36-Month	1095 days	1035-1155 days
48-Month	1460 days	1400-1520 days
60-Month	1825 days	1765-1885 days

i) INR Monitoring

All subjects will have INR monitoring performed at a minimum of every 28 days while on warfarin therapy. Warfarin dosage should be adjusted to ensure subjects are in the therapeutic range of 2.0 – 3.0, which is standard practice for subjects with non-valvular AF.

It is essential that investigators discuss the importance and value of the study required INR monitoring schedule with study subjects. INR values will be collected from subjects during follow-up visits, or directly from Coumadin Clinics, and reported by sites on the INR Log. While subjects are not required to have an INR during time off warfarin therapy, careful attention should be given to ensure compliance to the INR monitoring requirement of at least every 28 days once warfarin is restarted. Early discontinuation of warfarin therapy will be documented and the rationale provided on the case report form.

ii) 45-Day Office Visit

The 45-day visit will be scheduled such that the TEE occurs within 30-60 days post implant. Warfarin therapy and 81mg aspirin are to be maintained through the 45-day TEE.

During the visit a TEE will be conducted to assess the presence of LAA blood flow through and around the WATCHMAN device. If the TEE evaluation indicates complete LAA seal or residual blood flow around the margins of the WATCHMAN device in a retrograde or antegrade fashion, with jet size ≤ 5mm, the subject will discontinue warfarin therapy and begin adult aspirin regimen (325mg) once daily for the duration of the study, unless continuing on 81mg aspirin is medically necessary. Additionally, clopidogrel must also be started at this time and taken until the 6-month follow-up visit.

Alternatively, if the TEE evaluation indicates residual LAA blood flow with a jet size > 5mm around the margins of WATCHMAN device in either a retrograde or antegrade fashion, the subject should continue or reinitiate warfarin therapy until such time that LAA seal occurs or a jet size ≤ 5mm around the WATCHMAN device is observed. In this case aspirin will be continued at 81mg.

Additional information collected during the 45-day visit includes the following:

- INR values while on warfarin therapy
- TEE to assess device position, LAA seal, thrombus on the device surface, intracardiac thrombus and residual atrial septal shunt – to be conducted according to the Imaging Manual
- NIH Stroke Scale, Barthel Index, and Modified Rankin Scale
- Current medical status
- Current medication regimen
- Adverse events experienced since implant procedure

iii) 6 Month Visit

The 6 month visit will be conducted via telephone for those subjects with LAA seal or residual blood flow with jet size ≤ 5mm around the margins of the WATCHMAN device at the 45-day TEE. Subjects who had 45-day TEE evidence of LAA seal are expected to be on clopidogrel and aspirin therapy at the time of the visit. At completion of the 6-month visit, clopidogrel should be discontinued and subjects should remain on adult aspirin therapy indefinitely.

If a subject was unable to discontinue warfarin therapy due to jet size > 5mm at the 45-day TEE, the 6 month visit will be conducted via an office visit and the TEE will be repeated to assess seal around the WATCHMAN device. Subjects will be eligible to discontinue warfarin therapy only if the 6-month TEE confirms residual flow of ≤ 5mm around the device. In this scenario, warfarin would be discontinued and an adult daily aspirin prescribed indefinitely; Clopidogrel therapy would not be necessary to aid in the healing process after 6 months post implant.

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

- Collection of INR values for subjects who were on warfarin therapy during this time
- TEE (if required) to assess device position, LAA seal, thrombus on the device surface, intracardiac thrombus and residual atrial septal shunt – to be conducted according to the Imaging Manual
- Barthel Index and Modified Rankin Scale
- Current medical status
- Current medication regimen
- Serious adverse events and adverse events experienced since previous visit

iv) 12 Month Office Visit

Subjects will complete an office visit 12 months post implant with a TEE evaluation. Information collected during the 12-month visit includes the following:

- Collection of INR values for any subjects who continued on warfarin therapy beyond the 6 month visit
- TEE to assess device position, LAA seal, thrombus on the device surface, intracardiac thrombus and residual atrial septal shunt – to be conducted according to the Imaging Manual
- NIH Stroke Scale, Barthel Index, and Modified Rankin Scale
- Current medical status
- Current medication regimen
- Serious adverse events and adverse events experienced since previous visit

v) Additional Telephone Visits-18 Months and 30 Months

All subjects will complete a telephone visit at 18 months and 30 months.

At the 18 and 30-month visit the following information will be collected:

- Collection of INR values for any subjects who continued on warfarin therapy after the last visit
- Barthel Index and Modified Rankin Scale
- Current medical status
- Current medication regimen
- Serious adverse events and adverse events experienced since previous visit

vi) Annual Visits-2,3,4,5 Years

All subjects will complete an office visit at annual intervals. No additional TEEs are required after the 12-month visit. Information collected during the annual office visits includes the following:

- Collection of INR values for any subjects who continued on warfarin therapy
- NIH Stroke Scale, Barthel Index, and Modified Rankin Scale
- Current medical status
- Current medication regimen
- Serious adverse events and adverse events experienced since previous visit

11.9. *Study Completion*

Each subject will be followed for 5 years after the implant procedure.

12. Statistical Considerations

An overview of the adaptive study design, sample size and statistical analysis is provided below. Details on each aspect and methods for analyzing the study endpoints will be described in a separate Statistical Analysis Plan that will supersede this document.

12.1. *Sample Size Justification*

This is a prospective, multi-center non randomized continued access study with no formal pre-specified hypothesis test. All subjects will be followed for up to 5 years or until the study is terminated. Subjects enrolled in this study will be analyzed separately from the roll-in and randomized subjects enrolled in the PREVAIL study.

A sample size of up to 1500 subjects was chosen to assess incidence of rare events with a large degree of precision. **Table 12.1-1** provides the two-sided 95% confidence interval width assuming an event rate of 5%.

Table 12.1-1 Two-Sided Confidence Interval by Sample Size

Sample Size	95% CI Width
1000	2.8%
1250	2.5%
1500	2.3%

12.2. *Statistical Analysis*

Analysis will include all subjects enrolled into the study who undergo an attempted implant of the WATCHMAN device (i.e. undergo venous access with the intent of implanting the WATCHMAN device). While no formal hypothesis tests will be performed, descriptive statistics will be generated for the data collected at baseline, during the 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 are 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 leading to significant disability/death.

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.

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

14. 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

Per 21 CFR 812.150(a)(5) "The investigator shall notify the sponsor and the reviewing IRB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but in no event later than 5 working days after the emergency occurred"

Except in an emergency, prior written approval to deviate from the protocol should be obtained from the sponsor. Any deviation from the protocol must be recorded on the protocol deviation case report form and must provide the dates of and the reasons for each deviation.

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.

16. Device/Equipment Accountability

The sponsor will provide the WATCHMAN devices and access system to the investigator. These devices will be labeled as Investigational Use Only and will require special handling and storage controls. The devices must be kept in a secure location with restricted access. Devices are intended for use only by the investigator or sub-investigator(s). The investigator

is responsible to track the receipt, use and disposition of all investigational devices received, including lot/serial number and device model number.
WATCHMAN product associated with device deficiencies should be returned to BSC for analysis. If it is not possible to return the product, the investigator should document why the product was not returned and the final disposition of the product. Used product not associated with device deficiencies does not need to be returned to BSC but should be discarded according to hospital policy. Expired product should be returned to BSC and all unused product will be returned to BSC at the end of the study. Instruction for returning WATCHMAN product is included in the study regulatory binder.

17. Compliance

17.1. *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 IRB and/or regulatory authority has been obtained, if appropriate. Any additional requirements imposed by the IRB or regulatory authority shall be followed, if appropriate.

17.2. *Selection of Investigators*

Investigators will be selected for this study based upon training and experience. Investigators will have experience with the WATCHMAN device due to participation in previous WATCHMAN studies, PROTECT AF or PREVAIL.

The Investigator will ensure that this study is conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and that are consistent with GCP and applicable regulatory (local) requirements; whichever affords the greater protection to the subject.

17.2.1. 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.

17.2.2. 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 approval and discourse documentation. A copy of the IRB approval must be submitted to the sponsor

17.2.3. Investigator Reports

Table 17.2.3-1 Required Investigator Reports

Investigator Report	Submit To	Description
Unanticipated Adverse Device Effect (UADE)	Sponsor, IRB	Notification within ten working days after the investigator first learns of the event.
Withdrawal of IRB Approval	Sponsor	Notification within five working days.
Progress Report	Sponsor, IRB	The Investigator must submit this report at regular intervals, but not less than once per year.
Deviations from Investigational Plan	Sponsor, IRB	Report of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Notification within five working days.
Device use without Informed consent	Sponsor, IRB	Notification within five working days after the use occurs.
Final Report	Sponsor, IRB	Within three months of study termination or completion.

17.3. *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 IRB for written approval. A copy of the written IRB 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 IRB for all subsequent protocol amendments and changes to the Informed Consent form. The

Investigator must notify the IRB of deviations from the protocol or SAEs and UADEs occurring at the site in accordance with local procedures.

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

17.4. *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 research, as well as for additional purposes, such as overseeing and improving the performance of its device, new medical research and proposals for developing new medical products or procedures, and other business purposes. Information received during the study will not be used to market to subjects; subject names will not be placed on any mailing lists or sold to anyone for marketing purposes.

17.4.1. Role of Boston Scientific Representatives

Boston Scientific personnel can provide technical support to the investigator and other health care personnel (collectively HCP) as needed during implant, testing required by the protocol, and follow-ups. Support may include HCP training, addressing HCP questions, or providing clarifications to HCPs concerning the operation of BSC equipment/devices.

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

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

Boston Scientific personnel will not do the following.

- Practice medicine
- Provide medical diagnosis or treatment to subjects
- Discuss a subject's condition or treatment with a subject without the approval and presence of the HCP
- Independently collect critical study data (defined as primary or secondary endpoint data)

- Enter data in electronic data capture systems or on paper case report forms

17.4.2. 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

17.4.3. Sponsor Reports

Table 17.4.3-1 Required Sponsor Reports

Sponsor Report	Submit To	Description
Unanticipated Adverse Device Effect (UADE)	FDA, IRB, Investigators	Notification within ten working days after Sponsor first learns of the event.
Withdrawal of IRB Approval	FDA, IRB, Investigators	Notification within five working days after receipt of approval withdrawal.
Withdrawal of FDA Approval	IRB and Investigators	Notification will be made within 5 working days after receipt of the withdrawal of approval.
Current Investigator List	FDA	At 6 month intervals.

Progress Report	FDA, IRB, Investigators	Sponsor must submit this report at regular intervals, but not less than once per year.
Recall and Device Disposition	FDA, IRB, Investigators	Notification will be made within 30 working days after the request is made, and will include the reasons for any request that an investigator return, repair or otherwise dispose of any devices.
Final Report	FDA, IRB, Investigators	Sponsor will notify FDA within 30 working days of the completion or termination of the study. A final report will be submitted within 6 months after completion or termination.
Device use without informed consent	FDA	Notification will be made within 5 working days after receipt of notice from an investigator.

17.5. *Insurance*

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

18. Monitoring

Each clinical site will be monitored to ensure that the study is conducted in full compliance with the study protocol, and in accordance with the FDA Guideline for the Monitoring of Clinical Investigations, Good Clinical Practices, and the sponsor's policy and procedures, and the study Monitoring Plan.

Professionals qualified through training, education and experience will conduct the monitoring of the study. Contact the sponsor for additional information on the people responsible for monitoring.

The study may also be subject to a quality assurance audit by the sponsor 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.

19. Potential Risks and Benefits

19.1. *Risks Associated with the WATCHMAN Implant & Procedure*

Potential procedural risks associated with the WATCHMAN implant procedure are similar to those encountered peri- and postoperatively for many routine catheterization procedures. These include, but are not limited to, the following:

- Air embolism
- Allergic reaction, e.g. contrast media
- Anemia requiring transfusion
- Anesthesia risks and complications

- Arrhythmias
- Fistula, e.g. arteriovenous
- Cardiac perforation
- Cardiac tamponade
- Chest pain/discomfort
- Complete heart block
- Cranial bleed
- Death
- Endocarditis
- Gastrointestinal bleeding
- Groin puncture bleed
- Hematoma
- Hyper/Hypotension
- Infection
- Major bleeding requiring transfusion
- Myocardial infarction
- Pericardial effusion
- Pleural effusion
- Pneumothorax
- Pseudoaneurysm
- Pulmonary edema
- Pulmonary embolism
- Pulmonary vein obstruction
- Renal insufficiency/failure
- Respiratory insufficiency/failure
- Stroke
- Systemic embolism
- TEE complications, e.g. esophageal injury
- Thromboembolism
- Thrombosis
- Thrombosis at septal puncture
- Transient ischemic attack (TIA)
- Valvular damage
- Vascular damage
- Vasovagal reactions
- Wound dehiscence

Definitions of potential procedural related complications are located in **Table 25-1**.

In addition to the aforementioned general risks, additional risks specifically associated with the WATCHMAN implant are as follows:

- Additional surgery if the device is not placed in the correct position
- Allergic reaction to the implant materials

- Atrial septal shunt or iatrogenic atrial septal defect
- Device misplacement
- Device embolization
- Device fracture or extrusion
- Excessive bleeding
- Hypertrophic scarring or thrombosed veins
- Infection
- Device thrombosis
- Inability to move or retrieve device
- Inability to implant the device

19.2. *Possible Interactions with Concomitant Medical Treatments*

Subjects who receive the WATCHMAN device may stop Warfarin therapy as early as the 45-day follow-up visit if they meet Warfarin cessation guidelines; therefore, at that time, subjects may be at an increased risk of stroke. Warfarin is the proven standard of care for reducing the risk of stroke in atrial fibrillation. The WATCHMAN device is designed to be used instead of Warfarin. Thus, the absence of Warfarin may represent a risk, especially if the device is not effective in preventing stroke.

From the Warfarin package insert, risks associated with Warfarin therapy include:

- Major or fatal bleeding
- Risk factors for bleeding include: INR > 4.0, age 65 and older, high variable INRs, history of gastrointestinal bleeding, hypertension, cerebrovascular disease, serious heart disease, anemia, malignancy, trauma, renal insufficiency, concomitant drugs and long duration of warfarin therapy
- Hemorrhage from any tissue or organ
- Necrosis and/or gangrene of the skin or other tissues
- Epistaxis
- Bruising
- Prolonged bleeding from a cut or scrape
- Headache
- Nausea/upset stomach
- Vomiting
- Diarrhea
- Fever
- Skin rash
- Skin or tissue necrosis
- Decrease in white blood cell count
- Inability to tolerate the medication

19.3. *Risk Minimization Actions*

Efforts have been made to minimize these risks by clearly defining the subject inclusion/exclusion criteria and by ensuring that the treatment and follow-up of subjects are consistent with current medical practices. The WATCHMAN device is constructed of well-known, well-characterized materials and has undergone extensive mechanical functionality and clinical testing.

Investigational teams selected to conduct the study will be experienced and skilled in interventional cardiology and/or electrophysiology with trans-septal and left heart experience, will have training on the WATCHMAN LAA closure implant procedure and will have access to modern high technology medical facilities to conduct those procedures.

19.4. *Anticipated Benefits*

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. Economic and subject benefits related to the elimination of life-long compliance to Warfarin therapy and the frequent blood tests and lifestyle changes associated with blood thinning medications are numerous. Lastly, a device-based solution addressing the mechanism of stroke in atrial fibrillation subjects may prove to be simple, tolerable and cost-effective.

20. 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 the use of any investigational devices, study-required procedures and/or testing, or data collection.

The obtaining and documentation of Informed Consent must be in accordance with the principles of the Declaration of Helsinki, 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 IRB/EC. Any modification requires approval from BSC prior to use of the form. The ICF must be in a language understandable to the subject and if needed, BSC will assist the center in obtaining a written consent translation. Translated consent forms must also have IRB/EC approval prior to their use. Privacy language shall be included in the body of the form or as a separate form as applicable.

The process of obtaining Informed Consent shall:

- 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.

Study personnel should explain that even if a subject agrees to participate in the study and signs an Informed Consent for, TEE may demonstrate that the subject is not a suitable candidate for the study.

21. Safety Reporting

21.1. *Adverse Event Reporting*

For the purpose of this study an adverse event (AE) is an untoward event related to the study, the device, or the study procedures that affects the subject's health or safety. For the purposes of this study an Adverse Device Effect (ADE) is an adverse event related to the use

of the investigational medical device. When reporting an AE or ADE, the investigator will indicate the diagnosis of the event and correlating signs and symptoms on the adverse event report. 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.

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

- The WATCHMAN device
- The WATCHMAN implant procedure
- The use of study mandated medications including warfarin, clopidogrel or aspirin (i.e.,: gastrointestinal bleeding due to warfarin or an allergic reaction to clopidogrel)
- Any study required procedures (i.e., clinical complications from protocol required TEE)
- 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 the study endpoints of stroke, systemic embolization, death, etc.
- Thrombosis
- Bleeding complications requiring intervention or transfusion of blood
- Any potential UADE

Each adverse event will be evaluated by the investigator for relatedness and seriousness. Definitions of procedural related complications are located in **Table 25-1**.

i) Adverse Event Definitions

Adverse events should meet the reporting requirements in the preceding section before consideration for reporting as serious events.

Serious adverse events are to be reported to the sponsor within 1 business day of learning of the event. A serious adverse event (SAE) is an event that:

- Led to death
- Led to serious deterioration in the health of the subject that:
    - Resulted in a life-threatening illness or injury, or
    - Resulted in permanent impairment of a body structure or a body function, or

- Required in-subject hospitalization or prolongation of existing hospitalization, or
- Resulted in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or a body function

- Led to fetal distress, fetal death, or a congenital abnormality or birth defect

NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered a serious adverse event.

A serious adverse device effect (SADE) is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. All SAEs that could have led to a SADE if suitable action had not been taken or if circumstances had been less fortunate shall be reported as required by the local IRB or the protocol.

An unanticipated adverse device effect (UADE) is any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the protocol 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. If an adverse event is determined to meet the definition of an unanticipated adverse event, the sponsor will immediately conduct an evaluation. If an unanticipated adverse device effect that represents an unreasonable risk for subject health or a product performance failure becomes apparent, immediate action will be taken and the appropriate authorities will be notified. The investigator will be notified of the results of this evaluation. All unanticipated device-related adverse effects will be reported to all investigators.

21.2. *Stroke Reporting*

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

i. LA thrombus

ii. WATCHMAN Device Seal

iii. WATCHMAN Device thrombus or pannus

iv. Agitated saline contrast injection to evaluate presence of residual right to left shunt at the atrial level (persistence of PFO or residual puncture hole from transseptal catheterization for device placement)

v. Presence and grade of ascending and arch aortic atheroma

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

21.3. *Device Thrombus*

The most accurate determination of whether thrombus has formed on the surface of the WATCHMAN device is through TEE evaluation. In the case of thrombus on the atrial facing side of the device, anticoagulation therapy should be initiated for approximately 12 weeks or a longer period of time per hospital standard of care for treatment of thrombus. After the course of anticoagulation therapy a repeat TEE evaluation should be performed to confirm the thrombus has resolved[6]

21.4. *Boston Scientific Device Deficiencies*

A device deficiency is any inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunctions, misuse or use errors, and inadequate labeling. All device deficiencies will be documented and reported to BSC on the appropriate eCRF within one business day 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. Instructions for returning the investigational device(s) will be provided. 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.

21.5. *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, and regulatory authorities of UADE and SAE as required by local/regional regulations.

22. Committees

22.1. *Safety Monitoring Process*

To promote early detection of safety issues, the CAP 2 CEC will provide evaluations of safety events. Success of this program requires dynamic collection of unmonitored data as soon as the event is reported. This is expedited through Boston Scientific's Global Safety Office, which is responsible for coordinating the collection of information for the subject dossier from the centers. During regularly scheduled monitoring visits, clinical research

monitors will support the dynamic reporting process through their review of source document information.

22.2. *Clinical Events Committee*

A Clinical Events Committee (CEC) is an independent group of individuals with pertinent expertise that reviews and adjudicates important endpoints and relevant adverse events reported by study investigators. The CEC will review a safety event dossier, which may include copies of subject source documents provided by study centers. CEC responsibilities, qualifications, membership, and committee procedures are outlined in the CEC charter. The CECs classifications of the adverse events will be used in all study reports, evaluation of study endpoints and in all data analyses.

22.3. *Data and Safety Monitoring Board*

An independent Data and Safety Monitoring Board (DSMB) will be established for the review of data and safety parameters in the study. The DSMB will develop a charter and stopping rules for the study. The members will consist of at least four physicians in specialties of electrophysiology, interventional cardiology, or neurology. At least one member of the committee will be a biostatistician.

The DSMB will function in accordance with Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees. Meeting frequency will be determined by the DSMB to review the clinical data and assess the impact of adverse events.

The DSMB will be utilized to review data from the continued access study until the time of commercialization of the WATCHMAN device.

23. Suspension or Termination

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

23.1 Publication Policy

In accordance with the Corporate Policy on the Conduct of Human Subject Research, BSC requires disclosure of its involvement as a sponsor or financial supporter in any publication or presentation relating to a BSC study or its results. In accordance with the Corporate Policy for the Conduct of Human Subject Research, BSC will submit study results for publication (regardless of study outcome) following the conclusion or termination of the study. Boston Scientific Corporation adheres to the Contributorship Criteria set forth in the Uniform Requirements of the International Committee of Medical Journal Editors (ICMJE; http://www.icmje.org). In order to ensure the public disclosure of study results in a timely manner, while maintaining an unbiased presentation of study outcomes, BSC personnel may

assist authors and investigators in publication preparation provided the following guidelines are followed.

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

24. Bibliography

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25. Definitions

Table 25-1 Definitions

Term	Definition
Air embolism	Obstruction of the circulation by air that has gained entrance to vessels
Allergic reaction to contrast media	A response such as rash, hives, itching, asthma, hay fever, anaphylaxis, etc., to contrast media
Anemia requiring transfusion	A drop in hemoglobin that results in transfusion of 2 or more units of packed red blood cells
Anesthesia risks and complications	Complications and risks of general anesthesia include but are not limited to: difficulties with the lung, heart, and liver or nerve functions. Serious illness, additional surgery and even death may result from the complications of general anesthesia
Arrhythmias	An alteration in rhythm of the heartbeat that requires treatment with a device or anti-arrhythmic medication
AV fistula	A communication between an artery and vein in which arterial blood flows directly into a vein or is carried into a vein by a connecting pathway
Cardiac perforation/tamponade	See Pericardial Effusion
Chest pain/discomfort	Pressure, heaviness and/or sharp pain in the chest region
Complete heart block	Also known as third-degree heart block or complete AV block, it is a condition in which none of the electrical impulses can reach the ventricles
Cranial bleed	Asymptomatic intracranial bleed
Death	A death is defined as a cardiovascular death if the death is from a cardiovascular event including sudden death, MI, cardiac arrhythmia, and heart failure
Endocarditis	Inflammation of cardiac tissue (endocardium)
Gastrointestinal bleeding	Bleeding with an origin within the gastrointestinal system
Groin puncture bleed	Bleeding or oozing of blood from the groin access site used for the implant procedure
Hematoma	A mass of usually clotted blood that forms in a tissue, organ, or body space as a result of leakage from a blood vessel that requires additional treatment beyond applying pressure
Hyper/Hypotension	Elevated blood pressure exceeding 140 over 90 mmHg, or low blood pressures less than 90 over 50 mmHg

Term	Definition
Infection	The invasion of the body by pathogenic microorganisms and their multiplication which can lead to tissue damage and disease requiring treatment, e.g., endocarditis, pericarditis, sepsis
Major bleeding requiring transfusion	Non site-specific bleeding requiring the transfusion of 2 or more units packed red blood cells
Myocardial infarction	Either one of the following criteria satisfies the diagnosis for an acute, evolving or recent MI: 1) Typical rise and gradual fall (troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following: a) ischemic symptoms; b) development of pathological Q waves on the ECG; c) ECG changes indicative of ischemia (ST segment elevation or depression); or d) Coronary artery intervention (e.g. coronary angioplasty). 2) Pathologic findings of an acute MI
Pericardial effusion	Pericardial effusions are defined by the clinical therapy associated with the effusion. **Pericardial Effusion:** An observed pericardial effusion not necessitating percutaneous drainage nor surgical repair. **Pericardial Effusion with Tamponade:** A pericardial effusion resulting in percutaneous treatment/drainage. **Cardiac Perforation:** A pericardial effusion resulting in surgical intervention/repair.
Pleural effusion	Fluid in a pleural cavity
Pneumothorax	An abnormal state characterized by the presence of gas (as air) in the pleural cavity
Pseudoaneurysm	Extra-vascular fluid sac without vascular wall lining but with communication with arterial vessel
Pulmonary edema	Abnormal accumulation of fluid in the lungs
Pulmonary embolism	Embolism of a pulmonary artery or one of its branches that is produced by foreign matter and most often a blood clot originating in a vein of the leg or pelvis and that is marked by labored breathing, chest pain, fainting, rapid heart rate, cyanosis, shock, and sometimes death
Pulmonary vein obstruction	An obstruction in the pulmonary vein that can decrease blood flow to the atria
Renal insufficiency/failure	50% increase in creatinine level or requiring dialysis
Stroke	**Ischemic Stroke:** Sudden onset of a focal neurological deficit with symptoms and/or signs persisting more than 24 hours or symptoms less than 24 hours with

Term	Definition
	CT or MRI evidence of tissue loss without hemorrhage. **Hemorrhagic Stroke:** Symptomatic intracranial hemorrhage due to any cause.
Systemic embolism	Abrupt vascular insufficiency associated with clinical or radiologic evidence of arterial occlusion in the absence of other likely mechanisms (e.g., atherosclerosis, instrumentation). In the presence of atherosclerotic peripheral vascular disease, diagnosis of embolism to the lower extremities requires arteriographic demonstration of abrupt arterial occlusion.
Thromboembolism	The blocking of a blood vessel by a particle that has broken away from a blood clot at its site of formation
Thrombosis	The formation or presence of a blood clot within a blood vessel
Thrombosis at septal puncture	The formation or presence of a blood clot at the location of septal puncture during the implant procedure
Transient ischemic attack (TIA)	Acute focal neurological event (including focal motor deficit aphasia, difficulty walking, hemi sensory deficit, amaurosis fugax, blindness, or focal visual deficit) lasting at least 5 minutes and up to 24 hours that is imaging negative
Valvular damage	Damage to the valves within the heart
Vascular damage	Damage to the walls of the vessels
Vasovagal reactions	A fainting or loss of consciousness response generally due to a sudden drop in blood pressure, syncope, or other external stimuli
Wound dehiscence	The parting of the sutured lips of a surgical wound typically resulting from infection