WATCH-TAVR PROTOCOL

WATCHMAN FOR PATIENTS WITH ATRIAL FIBRILLATION UNDERGOING TRANSCATHETER AORTIC VALVE REPLACEMENT

Principal Investigators: Samir Kapadia MD, Martin Leon MD

Sponsor: Cleveland Clinic Investigator Initiated Trial

Funded by: Boston Scientific

Version Number: v4.4

July 9 2020

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Principal Investigator Protocol Approval Page

Study Title: WATCHMAN FOR PATIENTS WITH ATRIAL FIBRILLATION UNDERGOING TRANSCATHETER AORTIC VALVE REPLACEMENT

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I, the undersigned, have read and approve this protocol and agree on its content. It is confirmed that the information and guidance given in this protocol complies with scientific principles, the guidelines of Good Clinical Practice.

Principal Investigator Signature: S Kapadia 7/14/2020

Samir Kapadia, MD (Date)
Cleveland Clinic

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Principal Investigator Signature: Martin B. Leon MD 7/14/20

Martin Leon, MD (Date)
Columbia University Medical Center

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INVESTIGATOR PROTOCOL AGREEMENT

Study Title: WATCHMAN FOR PATIENTS WITH ATRIAL FIBRILLATION UNDERGOING TRANSCATHETER AORTIC VALVE REPLACEMENT

Version: V4.4

Study Sponsor: Cleveland Clinic Investigator Initiated Trial

By my signature, I

- Confirm that my staff and I have carefully read and understand this protocol or protocol amendment and are thoroughly familiar with the appropriate use of the device described herein.
- Agree to comply with the conduct and terms of the study specified herein and with any other study conduct procedures provided by the Sponsor (Cleveland Clinic).
- Agree to assume responsibility for the proper conduct of the study at this site.
- Agree not to implement deviations from or changes to the protocol or protocol amendments without agreement from the Sponsor (Cleveland Clinic) and prior submission to and written approval (where required) from the Institutional Review Board (IRB) except when necessary to eliminate an immediate hazard to the patients, or for administrative aspects of the study (where permitted by all applicable regulatory requirements).

_____ _____

Investigator's Signature Date

_____

Print Name

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LIST OF ABBREVIATIONS

AF: Atrial Fibrillation

AS: Aortic Stenosis

KCCQ: Kansas City Cardiomyopathy Questionnaire

mRS: Modified Rankin Scale

NIHSS: National Institute of Health Stroke Scale

QoL: Quality of Life

TAVR: Transcatheter Aortic Valve Replacement

VARC: Valve Academic Research Consortium

PROTOCOL SUMMARY

Title:	WATCHMAN for Patients With Atrial Fibrillation Undergoing Transcatheter Aortic Valve Replacement
Short Title:	WATCHMAN and TAVR
Objectives:	To evaluate the safety and effectiveness of the left atrial appendage occlusion with WATCHMAN Device in prevention of stroke and bleeding in patients with atrial fibrillation (AF) undergoing transcatheter aortic valve replacement (TAVR).
Endpoints	Primary Endpoint: Composite of all-cause mortality, stroke (ischemic and hemorrhagic), and bleeding (life-threatening and major) events. Secondary Endpoints: All-cause mortality, stroke (ischemic and hemorrhagic), bleeding (major and/or life-threatening as per VARC2 definitions), cardiovascular mortality, arterial or venous thrombosis or embolism, rehospitalization

	related to WATCHMAN procedure or device, QoL (KCCQ) at follow-up, and procedural costs for both TAVR and WATCHMAN.
Population:	The WATCHMAN device is FDA approved for stroke prevention in patients with non-valvular atrial fibrillation defined as "Atrial fibrillation in the absence of rheumatic mitral valvular heart disease". The current study aims to investigate the outcomes of implantation of the WATCHMAN device in patients with non-valvular AF undergoing FDA approved TAVR.
Phase:	IV
Number of Sites enrolling participants:	Approximately 33 US sites
Description of Study Agent:	The WATCHMAN device is a self-expanding left atrial appendage closure (LAAC) device with a porous covering on the proximal face. Device sizes: 21 mm, 24 mm, 27 mm, 30 mm, 33 mm
Study Design:	WATCH-TAVR is a prospective, multicenter, randomized event-driven controlled trial. Only centers with approval for commercial WATCHMAN implantation will be included in this trial. Subjects will be enrolled at approximately 33 centers in the United States. There will be approximately 350 subjects enrolled, with 175 patients being randomized to TAVR + medical therapy and 175 patients randomized to simultaneous TAVR+WATCHMAN to accumulate the 191 primary events needed. Patients with non-valvular AF undergoing standard of care TAVR will be enrolled in the trial. Patients randomized to receive the WATCHMAN device will receive anticoagulation with warfarin and aspirin for 6 weeks after the procedure. After 6 weeks, the plan of care will follow WATCHMAN labeling. Patients randomized to the TAVR + medical therapy arm will be treated in accordance with standard of care with either warfarin, other anticoagulant/antiplatelet therapy, or no anticoagulation at the discretion of the treating physician. All patients will continue to receive routine post-TAVR follow-up and care. Patients will be monitored for primary and secondary endpoints as outlined. Baseline information and laboratory data will be collected as described in the protocol.
Selection Criteria	Inclusion Criteria: Determination for participation in the study is based upon standard of care practice for assessment of TAVR & WATCHMAN eligibility. 1. Men and Women ≥ 18 years of age

2. The patient meets criteria for and is eligible to undergo TAVR procedure
3. The patient has documented paroxysmal, persistent, or permanent atrial fibrillation
4. The patient meets the WATCHMAN labeling guidelines and is eligible to undergo the WATCHMAN implantation procedure
5. The patient is eligible for short term warfarin therapy
6. The patient or legal representative is able to understand and willing to provide written informed consent to participate in the trial
7. The patient is able and willing to return for required follow-up visits and examinations

Exclusion Criteria:

1. The patient had a stroke or TIA within the last 6 months prior to enrollment
2. Contraindication for short term anticoagulation
3. Moderate or severe MS with mean gradient across MV >10 mm Hg of MVA < 1.2cm^2.
4. The patient has symptomatic carotid disease (i.e., carotid stenosis ≥ 50% associated with ipsilateral transient or visual TIA evidenced by amaurosis fugax, ipsilateral hemispheric TIAs or ipsilateral stroke within 6 months)
5. Prior occlusion of LAA
6. The patient has an implanted mechanical mitral valve
7. The patient *requires* long-term warfarin therapy due to:
    a. Secondary to conditions such as prior arterial embolism or other indications such as pulmonary embolism or deep vein thrombosis within the previous 6 months
    b. The patient is in a hypercoagulable state; exclude the patient if per medical record documentation, the patient meets any of the following criteria:
        - Thrombosis occurring at under 40 years age
        - Idiopathic or recurrent VTE (venous thromboembolism)
        - Thrombosis at an unusual site (cerebral veins, hepatic veins, renal veins, IVC, mesenteric veins)
        - Family history of VTE or of inherited prothrombotic disorder, recurrence/extension of thrombosis while adequately anti-coagulated
8. The patient is actively enrolled in another trial of a cardiovascular device or an investigational drug (post-market study participation and registries are acceptable)

9. The patient is pregnant or pregnancy is planned during the course of the investigation if patient is of child bearing potential
10. Any clinically significant medical condition or presence of any laboratory abnormality performed prior to randomization that is considered by the investigator to be clinically important and could interfere with the conduct of the study or not meeting procedure guidelines for TAVR or WATCHMAN
11. The patient has a life expectancy of less than two years

Participant Duration: 2 Years

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1 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

1.1 BACKGROUND INFORMATION

Atrial fibrillation (AF) is a common baseline comorbidity and the commonest arrhythmia in patients with aortic stenosis (AS) undergoing Transcatheter Aortic Valve Replacement (TAVR). AF is a known risk factor for stroke during or after TAVR, associated with stroke, bleeding complications, worse outcomes and increased mortality[1]. The TAVR population is at increased long-term bleeding risk, with cognitive impairment, high risk of falls, history of spontaneous bleeding, etc. Standard medical therapy for emboli prevention in AF, long term oral anticoagulation (OAC), carries risk of hemorrhagic stroke, as well as major bleeding complications[2]. Anti-platelets prescribed after TAVR, combined with OAC, worsen bleeding risk further[3]. Left atrial appendage closure is an alternative to OAC, which obviates the need for regular medication and frequent monitoring. The WATCHMAN Left Atrial Appendage Closure (LAAC) System is the only device that has been approved by the FDA for preventing thrombo-embolic events in patients with non-valvular atrial fibrillation (AF)[4]. Non-valvular AF is defined as atrial fibrillation in the absence of rheumatic mitral valvular heart disease[5]. The WATCHMAN device has shown improved safety compared to OAC, with reduced event rates for hemorrhagic stroke and major bleeding in patients receiving the implant[6,7]. There are only small reports of feasibility of the procedure[8]. Randomized trials with the WATCHMAN device have excluded patients with valvular heart disease. As a result, data on safety and efficacy of the device in TAVR patients with AF is lacking[9].

1.2 RATIONALE

The WATCH-TAVR study aims to investigate the safety and efficacy of the WATCHMAN device in patients with AF who have severe AS and are undergoing TAVR. In addition, the simultaneous procedure arm aims to combine two device-related procedures into one single procedure, thereby exposing the patient to only one hospitalization and general anesthesia, potentially reducing risks in an already elderly and frail population. The combined procedure also allows a common venous access to be obtained for temporary pacing and delivery of the WATCHMAN device. The combined procedure, OR time, TEE and fluoroscopy may reduce costs to the patient. The trial is feasible and has the potential to have impactful and practice changing results.

1.3 POTENTIAL RISKS AND BENEFITS

1.3.1 KNOWN POTENTIAL RISKS

Potential surgical risks associated with the WATCHMAN implant procedure are similar to those encountered peri- and postoperatively for many routine catheterization procedures.

In addition to the general surgical 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
- Device misplacement
- Device embolization
- Device fracture or extrusion
- Excessive bleeding
- Hypertrophic scarring or thrombosed veins
- Inability to move or retrieve device

Patients who receive the WATCHMAN implant should stop warfarin therapy at the 45-day follow-up visit; therefore, at that time, patients may be at an increased risk of stroke. Warfarin is the proven standard of care for reducing the risk of stroke in atrial fibrillation.

Risks associated with long term warfarin therapy are:

- Fatal or nonfatal hemorrhage from any tissue or organ
- Bleeding which occurs when PT/INR is within the therapeutic range warrants diagnostic investigation since it may unmask a previously unsuspected lesion, e.g., tumor, ulcer, etc.
- Necrosis of skin and other tissues.
- See ADVERSE REACTIONS section of warfarin tablets package insert.

1.3.2 KNOWN POTENTIAL BENEFITS

The WATCHMAN device has been FDA approved to prevent thrombo-embolic events originating from the LAA. However trials with the WATCHMAN device have excluded any patient with an Aortic Valve Area < 1.0 cm^2. In patients with AS, the primary site of thrombus origin has been demonstrated to be the LAA. This makes the WATCHMAN device potentially beneficial in stroke prevention for patients with AS. The device also has improved safety compared to oral anticoagulation, with less bleeding and hemorrhagic stroke rates.

The simultaneous TAVR and WATCHMAN procedure will share anesthesia time, OR time, TEE and hospital admission costs. By avoiding two separate general anesthesia events, risks to the patient are reduced. Risks of bleeding associated with two separate intra-procedure heparinization are also avoided.

Long term oral anticoagulation carries with it an elevated risk of bleeding. The general population of patients undergoing TAVR are elderly and have high frailty scores, increasing risks of bleeding further. Device based thrombo-embolism prevention will avoid these increased bleeding risks and possibly improve quality of life. It will also obviate the need for regular medication, decrease drug-drug interactions in a population already on multiple medications, and reduce the need for regular monitoring of INR levels.

2 OBJECTIVES AND PURPOSE

The WATCH-TAVR study is designed to evaluate the safety and effectiveness of left atrial appendage occlusion with the WATCHMAN device in the prevention of stroke and bleeding in patients with atrial fibrillation undergoing transcatheter aortic valve replacement (TAVR).

The efficacy of the WATCHMAN device has been previously demonstrated in patients with non-valvular AF who are eligible for warfarin therapy. Until now, trials with the WATCHMAN device have excluded patients with aortic stenosis (AVA <1.0cm^2). There is no conclusive evidence of the benefit of the device in patients with severe AS. A large portion of patients with severe AS who undergo TAVR are known to have AF. This increases stroke risk dramatically after the procedure and is associated with worse outcomes. Standard medical therapy, i.e. anticoagulation is associated with increased risks of bleeding, including major bleeds and intra-cranial hemorrhage. There is a lack of clear consensus guidelines regarding the use of anticoagulation in AF after TAVR. In addition, many patients are unsuitable candidates for long term anticoagulation and need an alternative approach to stroke prevention. This study aims to establish the efficacy and safety of the WATCHMAN device in preventing stroke and bleeding in patients with AF undergoing TAVR.

3 STUDY DESIGN AND ENDPOINTS

3.1 DESCRIPTION OF THE STUDY DESIGN

The WATCH-TAVR study is a prospective, multicenter, randomized trial to be conducted at approximately 33 centers in the U.S. The trial aims to enroll approximately 350 patients to accumulate the necessary 191 primary events. Enrollment is expected to occur over the course of 18 months. Patients will be followed up for a total of 2 years.

Eligible patients from each investigator's patient population shall be screened as potential candidates for the WATCH-TAVR study. The patient's history and baseline clinical parameters will be reviewed and written informed consent to participate will be obtained. The fulfillment of all inclusion and exclusion criteria shall be assessed and further baseline parameters necessary prior to randomization shall be obtained. Patients will be randomized to TAVR procedure alone or TAVR procedure combined with the WATCHMAN procedure. Determination for participation in the study is based upon standard of care practice for assessment of TAVR & WATCHMAN eligibility.

It is recommended that the procedure (TAVR or combined WATCHMAN + TAVR) should be performed within two weeks of randomization. All patients who receive the WATCHMAN device will follow the WATCHMAN Device Implant Pharmacologic Regimen (see section 6.2.4). Patients randomized to the TAVR procedure only will be treated in accordance with standard of care with either warfarin, other anticoagulant/anti-platelet therapy, or no anticoagulation at the discretion of the treating physician. All patients will continue to receive routine post-TAVR follow-up and care. Use of the WATCHMAN device in the TAVR only arm should be avoided during the first year, unless medically necessary. All enrolled study patients shall be followed up at 45 days, 6 months, 12 months and 24 months. Follow-up beyond 1 year may be in the form of an office visit or a phone call.

Patients shall be evaluated for neurological function by NIH Stroke Scale and for modified Rankin Scale (MRS) stroke disability at baseline and each visit. In addition all patients who experience a Stroke or TIA will be evaluated by a neurologist and have brain imaging.

3.2 PRIMARY ENDPOINT

Composite of all-cause mortality, stroke, life- threatening, and major bleeding events.

3.3 SECONDARY ENDPOINTS

All-cause mortality, stroke (ischemic and hemorrhagic), bleeding (major and/or life-threatening as per VARC2 definitions), cardiovascular mortality, arterial or venous thrombosis or embolism, rehospitalization related to the WATCHMAN procedure or device, QoL (KCCQ-12) at follow-up, and procedural costs related to the initial TAVR and WATCHMAN procedures.

4 STUDY ENROLLMENT AND WITHDRAWAL

4.1 PARTICIPANT INCLUSION CRITERIA

The WATCH-TAVR study will include patients who fulfill the following criteria: Determination for participation in the study is based upon standard of care practice for assessment of TAVR & WATCHMAN eligibility.

1. Men and Women ≥ 18 years of age
2. The patient meets criteria for and is eligible to undergo TAVR procedure
3. The patient has documented paroxysmal, persistent, or permanent atrial fibrillation
4. The patient meets the WATCHMAN labeling guidelines and is eligible to undergo the WATCHMAN implantation procedure
5. The patient is eligible for short term warfarin therapy
6. The patient or legal representative is able to understand and willing to provide written informed consent to participate in the trial
7. The patient is able and willing to return for required follow-up visits and examinations

4.2 PARTICIPANT EXCLUSION CRITERIA

Any patient who fulfills any of these criteria shall be excluded:

1. The patient had a stroke or TIA within the last 6 months prior to enrollment
2. Contraindication for short term anticoagulation
3. Moderate or severe MS with mean gradient across MV >10 mm Hg or MVA < 1.2cm^2.

4. The patient has symptomatic carotid disease (i.e., carotid stenosis ≥ 50% associated with ipsilateral transient or visual TIA evidenced by amaurosis fugax, ipsilateral hemispheric TIAs or ipsilateral stroke within 6 months)
5. Prior occlusion of LAA
6. The patient has an implanted mechanical mitral valve
7. The patient requires long-term warfarin therapy due to:
    a. Secondary to conditions such as prior arterial embolism or other indications such as pulmonary embolism or deep vein thrombosis within the previous 6 months
    b. The patient is in a hypercoaguable state; exclude the patient if per medical record documentation, the patient meets any of the following criteria:
        - Thrombosis occurring at a young age (i.e. less than 40 y/o)
        - Idiopathic or recurrent VTE (venous thrombo-embolism)
        - Thrombosis at an unusual site (cerebral veins, hepatic veins, renal veins, IVC, mesenteric veins)
        - Family history of VTE or of inherited prothrombotic disorder, recurrence/extension of thrombosis while adequately anticoagulated
8. The patient is actively enrolled in another trial of a cardiovascular device or an investigational drug (post-market study participation and registries are acceptable)
9. The patient is pregnant or pregnancy is planned during the course of the investigation if patient is of child bearing potential
10. Any clinically significant medical condition or presence of any laboratory abnormality prior to randomization that is considered by the investigator to be clinically important and could interfere with the conduct of the study or not meeting procedure guidelines for TAVR or Watchman
11. The patient has a life expectancy of less than two years

4.3 SUBJECT SELECTION

All patients undergoing TAVR who are in AF shall be considered as potential candidates for the trial. Patients who potentially fulfill the inclusion and exclusion criteria will be informed in detail about the study and invited to participate. Prior to any study assessments or procedures, the patient will be asked to read and sign the informed consent form (ICF). Patient eligibility can be determined if all inclusion and no exclusion criteria have been met, after which randomization may take place.

4.4 PARTICIPANT WITHDRAWAL OR TERMINATION

All subjects have the right to withdraw from treatment or study participation without prejudice. The investigator can discontinue any subject at any time if medically necessary, although every effort should be made to follow the subjects until study completion. At a minimum, vital status on every subject should be ascertained at study completion. It will be documented whether or not each subject completed the clinical study.

Reasons that a subject may discontinue participation in a clinical study are considered to constitute one of the following:

- Death
- Subject withdrew consent
- Physician decision
- Lost to follow-up

5 STUDY DEVICE

5.1 STUDY DEVICE DESCRIPTION

The WATCHMAN LAAC device is permanently implanted at or slightly distal to the LAA ostium. It is delivered using a standard transseptal catheterization technique in a catheterization laboratory or cardiovascular operating room setting. It is designed to prevent emboli from the LAA and thus prevent ischemic stroke and thromboembolism in patients with atrial fibrillation who are at risk for LAA thrombi. The device can be implanted during the TAVR procedure, potentially using the site of the temporary pacemaker for access.

The WATCHMAN LAA Closure Technology consists of:

- WATCHMAN LAA Closure Device (also referred to as “WATCHMAN Device”, “WATCHMAN LAAC Device”)
- WATCHMAN Delivery System (consisting of Delivery Catheter and loaded Implant)
- WATCHMAN Access System (consisting of Access Sheath and Dilator)

The WATCHMAN LAAC Device is the implantable component of the WATCHMAN LAAC Technology. It is composed of a self-expanding nitinol structure with a porous membrane on the proximal face. The implant is delivered to the Left Atrial Appendage by femoral venous access and transseptal puncture to enter the left atrium.

Device sizes: 21 mm, 24 mm, 27 mm, 30 mm, 33 mm.

6 STUDY PROCEDURES AND SCHEDULE

6.1 STUDY PROCEDURES/EVALUATIONS

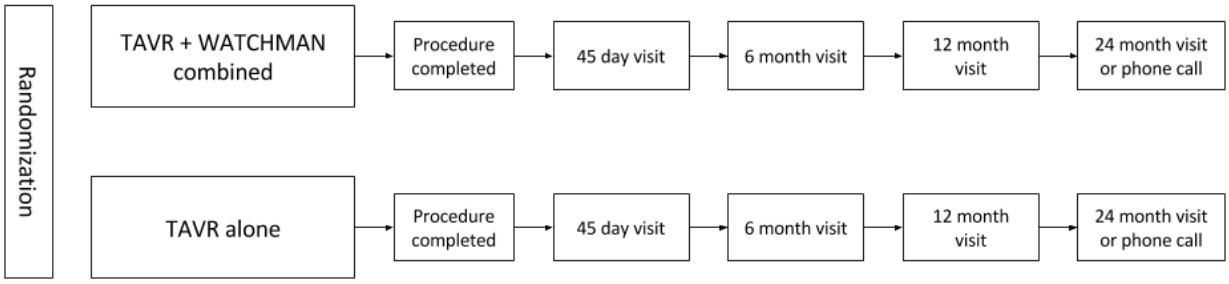
6.1.1 STUDY PROCEDURES

The time course for the trial is divided into a treatment period and follow-up period. Patients will be randomized in a 1:1 allocation ratio to the following treatment arms:

- TAVR alone (n=175)
- TAVR and WATCHMAN (n=175)

Follow-up will commence once the treatment period is completed. Patients will be followed up to 2 years from treatment procedure completion.

Scheme of subject's participation in study



6.2 STUDY SCHEDULE

6.2.1 STUDY REQUIREMENTS

STUDY REQUIREMENTS FOR TAVR/WATCHMAN COMBINED PROCEDURE

STUDY REQUIREMENTS TAVR/WATCHMAN COMBINED ARM					
	Baseline	**45 days after Combined Procedure (+/- 15 d)**	**6 Months after Procedure (+/- 1 month)**	**12 Months after Procedure (+/- 1 month)**	**24 Months after Procedure[1] (+/- 1 month)**
	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**
Informed Consent	+				
Inclusion/Exclusion Criteria	+				
Randomization	+				
WATCHMAN Procedure	+				
TEE[2]	+ (during WATCHMAN procedure)	+			
KCCQ-12 Score	+	+	+	+	+
Vital Signs	+	+	+	+	
AE Monitoring	+	+	+	+	+
INR	+	+	+[3]	+[3]	+[3]
Blood Work	+[4]				
NIH Stroke Scale (NIHSS	+	+	+	+	+
Modified Rankin Scale (MRS)	+	+	+	+	+
Brain Image (CT or MRI)[5]	As Required				
Neuro Assessment[6]	As Required				

1 May be visit or phone follow up
2 TEE During the WATCHMAN procedure and 45 days (+/-15 days) after the WATCHMAN Procedure. Patients randomized to WATCHMAN who have intracardiac thrombus visualized are contraindicated from receiving the device per labeling guidelines, but will remain in the trial as intent to treat and should be followed for all study visits.
3 If patient continues to be on warfarin
4 Tests include serum creatinine, platelet count and hemoglobin level. To be obtained within 7 days of randomization/WATCHMAN procedure
5 Required following a Stroke or TIA event including neurological assessment by a Neurologist.
6 Neurological assessment by neurologist if a patient experiences a stroke or TIA throughout the duration of the study

STUDY REQUIREMENTS FOR TAVR PROCEDURE ALONE

STUDY REQUIREMENTS TAVR PROCEDURE ALONE (MEDICAL TREATMENT) ARM					
	Baseline	**45 days after TAVR procedure (+/- 15 d)**	**6 Months after procedure (+/- 1 month)**	**12 Months after procedure (+/- 1 month)**	**24 Months after procedure [1] (+/- 1 month)**
	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**
Informed Consent	+				
Inclusion/Exclusion Criteria	+				
Randomization	+				
KCCQ-12 Score	+	+	+	+	+
Vital Signs	+	+	+	+	
AE Monitoring	+	+	+	+	+
INR	+	+	+	+	+[2]
Blood Work	+[3]				
NIH Stroke Scale (NIHSS	+	+	+	+	+
Modified Rankin Scale (MRS)	+	+	+	+	+
Brain Image (CT or MRI)[4]	As Required				
Neuro Assessment[5]	As Required				

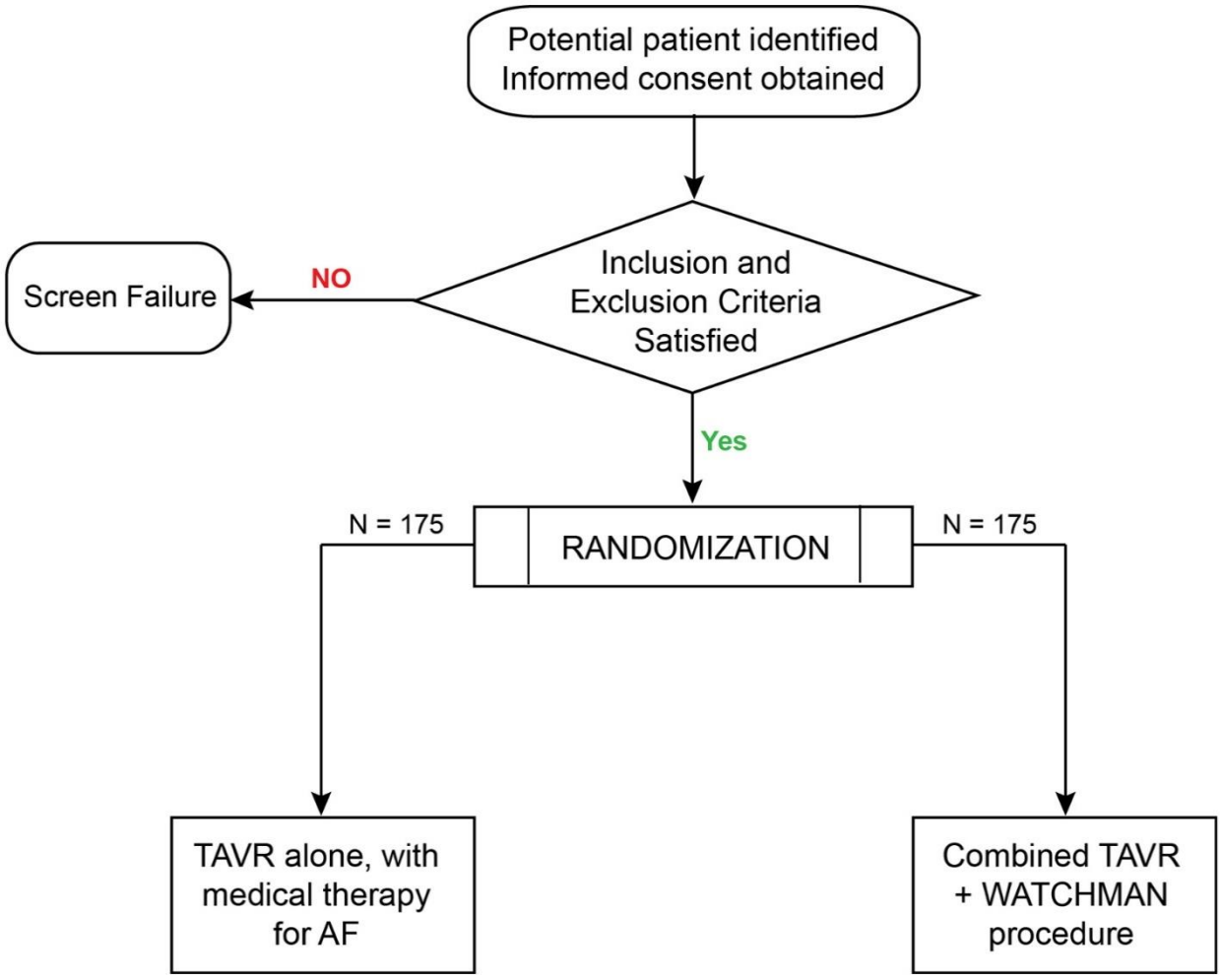
1May be visit or phone follow up
2 If patient continues to be on warfarin
3 Tests include serum creatinine, platelet count and hemoglobin level. To be obtained within 7 days of randomization and within 7 days of WATCHMAN (same lab may be used if 7 day criteria met)
4 Required following a Stroke or TIA event including neurological assessment by a Neurologist.
5 Neurological assessment by neurologist if a patient experiences a stroke or TIA throughout the duration of the study

6.2.2 ENROLLMENT

All Patients who are to undergo a TAVR procedure and have non-valvular AF are eligible for screening as potential candidates for the study.

Patients who provide consent and satisfy all the inclusion and exclusion criteria will be eligible for randomization.

PATIENT ENROLLMENT OVERVIEW



6.2.3 FOLLOW-UP

Patients will have follow-up visits at 45 days following the TAVR procedure alone or post-WATCHMAN implant, and 6 months, 12 months and 24 months post -procedure. During each follow-up visit (scheduled or interim), all enrolled patients must be evaluated for adverse events using an assessment of history and physical exam. NIHSS Stroke Assessment Worksheet and MRS Stroke Assessment Worksheet should be completed at each visit.

For patients who suffer a stroke or TIA following randomization, the following assessments should be completed:

- Complete evaluation by Neurologist, AND
- Brain Imaging (CR/MRI)

Patients who received a WATCHMAN implant are required to undergo a TEE examination during the procedure and 45-days post-implant. TEE imaging must be performed in accordance with standard protocol, using color Doppler technology and possibly ECHO contrast within the LAA to confirm the absence of blood flow AROUND and/or THROUGH the WATCHMAN implant. Patients randomized to WATCHMAN who have intracardiac thrombus visualized during the procedure are contraindicated from receiving the device per labeling guidelines, but will remain in the trial as intent to treat and should be followed for all study visits.

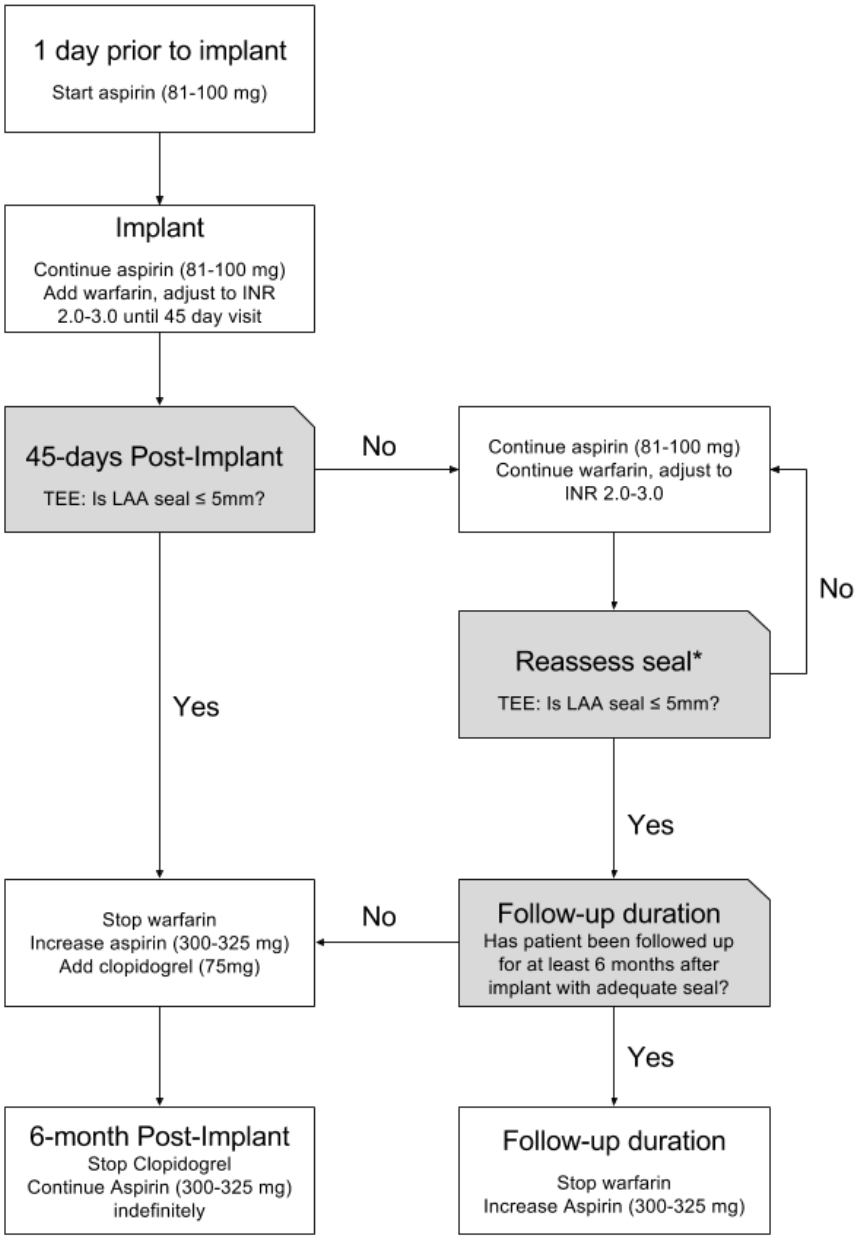
Completion of the following assessments must be documented on the Follow-Up Case Report Form:

- The presence or lack of flow in the LAA;
- Residual atrial septal shunt;
- Thrombus on the device surface;
- Device position

Patients randomized to the TAVR alone group are to remain on anticoagulant/antiplatelet therapy at the discretion of the treating physician indefinitely if possible. If the patient is on warfarin, dosage should be adjusted such that patients maintain a therapeutic INR of 2.0 – 3.0. According to ACC/AHA/ESC Guidelines on Management of Patients with Atrial Fibrillation, INR is to be monitored per site standard of care guidelines while patients are on warfarin therapy.

All patients should continue to undergo routine post-TAVR follow-up as per accepted standards of care.

6.2.4 WATCHMAN DEVICE IMPLANT PHARMACOLOGIC REGIMEN



Post-procedure warfarin therapy is required in ALL patients receiving a WATCHMAN Device. Patients should be placed on 81-100 mg of aspirin and warfarin titrated to post-implant INR 2.0-3.0. At 45 days (±15 days) post-implant, WATCHMAN Device assessment is to be performed via TEE. Cessation of warfarin is at physician discretion provided that any peri-device flow demonstrated by TEE is ≤5 mm. If adequate seal is not demonstrated, subsequent warfarin cessation decisions are contingent on demonstrating flow ≤5 mm. At the time the patient ceases warfarin, the patient should begin clopidogrel 75 mg daily and increase aspirin to 300-325 mg daily. This regimen should continue until 6 months have elapsed after implantation. Patients should then remain on aspirin 300-325 mg indefinitely. If a patient remains on warfarin and aspirin 81 mg for at least 6 months after implantation, and then ceases warfarin, the patient should not require clopidogrel, but should increase aspirin to 300-325 mg daily, which then should be continued indefinitely.

* Timing of re-evaluation of LAA seal by TEE is per physician's discretion and according to standard of care.

7 ASSESSMENT OF SAFETY

7.1 SPECIFICATION OF SAFETY PARAMETERS

Because all of the devices and interventions for this study are FDA approved, if a subject experiences an adverse event that the investigator feels is related to a device or intervention, site staff should follow the standard reporting procedures as outlined in the manufacturer's product labeling and/or as required by applicable country regulations.

The Medical Monitor will review safety data for the study and provide study oversight as necessary (see Medical Monitor Charter for details).

7.2 ADVERSE EVENT REPORTING

An adverse event is an untoward event that affects the patient's health or safety. When reporting an adverse event, the investigator will complete the AE report form.

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 TAVR device
- The WATCHMAN implant procedure (including pericardial effusion, device embolism, stroke)
- The TAVR implant procedure (including pericardial effusion, device embolism, stroke)
- Any study required procedures (i.e., clinical complications from protocol required TEE, etc.)

The following adverse events will also be reported regardless of relationship to the device(s) or procedure(s):

- Any event with an outcome of death
- Stroke (ischemic and/or hemorrhagic) and TIA
- Any events associated with bleeding
- Arterial or venous thrombosis or embolism
- Rehospitalization related to procedure or device implantation
- Any potential Unanticipated Adverse Device Effects (see definition below)

Each adverse event will be evaluated by the investigator for relatedness and seriousness.

i) Relatedness

The relatedness of an adverse event to the study, WATCHMAN Device, TAVR device, WATCHMAN procedures or TAVR procedure will be assessed by the Investigator for each submitted adverse event form.

- **Device Related**: An adverse event that results from the presence or performance of the device or any other component of the system.

- **Procedure Related**: An adverse event that occurs due to the system implantation procedure. Adverse events that are contributable to the anesthesia or contrast media given during the implant procedure will be considered procedure related.
- **Unknown**: An adverse event that cannot be determined to have a causal relationship with either the system or procedure will be classified as unknown.
- **Not Related**: An adverse event that is determined to not have a causal relationship with either the system or procedure.

ii) Seriousness

Adverse events as described above will be evaluated for serious injury. Adverse events resulting in death or serious injury are to be reported to the sponsor within 24 hours of learning of the event. Serious injury is an injury or illness that:

- Is life-threatening, or
- Results in permanent impairment of a body function or permanent damage to a body structure, or
- Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure. Permanent means irreversible impairment or damage to a body structure or function, excluding trivial impairment or damage [21 CFR 803.3]

Note: Not all cosmetic damage is considered trivial. Furthermore, a life-threatening injury meets the definition of serious injury, regardless of whether the threat was "temporary." It should also be noted that a device does not have to malfunction for it to cause or contribute to a serious injury. Even though a device may function properly, **it can still cause or contribute to a death or serious injury. Caused or contributed to** means that a death or serious injury was or may have been attributed to a medical device or that a medical device was or may have been a factor in a death or serious injury, including events occurring as a result of [21 CFR 803.3]: 1. Failure; 2. Malfunction; 3. Improper or inadequate design; 4. Manufacture; 5. Labeling; or 6. User error

Unanticipated Adverse Device Effect (UADE)

Per 21 CFR 812.3(s) "an unanticipated adverse device effect means any serious adverse effect on health or safety or any life-threatening problem or death caused by or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of patients."

8 CLINICALMONITORING

The Sponsor or designee has ethical, legal and scientific obligations to carefully follow this study in accordance with established research principles and applicable regulations. The investigator, as part of his responsibilities, is expected to cooperate with the Sponsor or designee in ensuring that the study adheres to the protocol and GCP requirements.

As part of a concerted effort to fulfill these obligations, monitoring will be carried out during the study in accordance with the Monitoring Plan set forth for this trial.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL AND ANALYTICAL PLANS

All statistical analysis will be "intent-to-treat", with each patient being considered as part of their randomized group irrespective of the actual treatment received. Patients not having an event, or lost to follow-up will be censored at the time of their last documented follow-up visit or phone call.

The study is designed to demonstrate the non-inferiority of the WATCHMAN device compared to the control group, with regards to the primary endpoint (composite of all-cause mortality, stroke (ischemic and hemorrhagic), or bleeding (major and/or life-threatening)). Non-inferiority will be assessed using the 1-sided 97.5% confidence interval around the hazard ratio (WATCHMAN-TAVR: TAVR only). Non-inferiority will be demonstrated if the 1-sided 97.5% upper confidence limit for the difference in proportions is less than 1.5. If the non-inferiority objective is met, additional analyses to assess superiority of the WATCHMAN group to the control group will be performed. The composite primary endpoint will also be summarized as events per 100 patient-years of follow-up.

For data collected at baseline, during the procedure and at follow-up, descriptive statistics will be generated. Continuous variables will be summarized with reporting of mean, standard deviation (SD), median, interquartile range (Q1, Q3) and range (minimum and maximum). General linear models will be used to compare continuous variables across treatment groups. Categorical variables will be summarized using counts and percentage of subjects and compared using the standard Chi-square statistic or Fisher's Exact test, as appropriate.

In general, missing data will not be imputed and will remain missing, unless otherwise indicated.

9.2 STATISTICAL HYPOTHESES

The study is designed to demonstrate the non-inferiority of the WATCHMAN device compared to the control group, with regards to the primary endpoint (composite of all-cause mortality, stroke (ischemic and hemorrhagic), bleeding (major and/or life-threatening)).

The following null hypotheses will be tested:

- H_{01}: The hazard ratio for WATCHMAN + TAVR relative to TAVR is ≥ 1.5 (non-inferiority)
- H_{02}: The hazard ratio for WATCHMAN + TAVR relative to TAVR is ≥ 1.0 (superiority)

If H_{01} is rejected, then H_{02} will also be tested. If the null hypothesis for non-inferiority is not rejected, H_{02} will not be tested.

9.3 ANALYSIS POPULATIONS

Intention-to-Treat Population (ITT): The primary analysis will be based on the ITT population. All randomized subjects will be analyzed according to their original randomization assignment (WATCHMAN+TAVR or TAVR) regardless of treatment received.

Per-protocol population: The per-protocol population is defined as patients in the WATCHMAN groups who received both the WATCHMAN and the prosthetic valve. In the TAVR only group, it is defined as patients who had the prosthetic valve placed.

9.4 DESCRIPTION OF STATISTICAL METHODS

9.4.1 GENERAL APPROACH

The ITT population will be used to analyze the primary and secondary endpoints. The non-inferiority hypothesis will only be tested using the primary endpoint of all-cause mortality, stroke, and major/life-threatening bleeding. Event rates, hazard ratio and 95% confidence intervals and a p-value associated with the non-inferiority hypothesis will be provided. If the non-inferiority objective is met, a p-value for the superiority hypothesis will also be provided. Secondary endpoints will be summarized using event rates, hazard ratios and 95% confidence intervals. Nominal p-values for comparisons between treatment groups will be provided for descriptive purposes only.

All patients should be followed until the termination of the study, regardless of adherence to the treatment strategy. Available information on patients lost to follow-up will be included in the analyses. Patients not reaching a primary endpoint by the time of study termination will be censored at their last known assessment.

Statistical methods will be further outlined in the Statistical Analysis Plan (SAP).

9.4.2 ANALYSIS OF THE PRIMARY ENDPOINT

The primary endpoint is the first occurrence of all-cause mortality, stroke or major/life-threatening bleeding event within one year following randomization. Estimates of the hazard ratio and 95% confidence intervals will be based on the Cox proportional hazards model, under the assumption of proportional hazards. Comparison of cumulative hazard functions will be based on the log-rank test.

The upper bound of the confidence interval will be generated from the Cox proportional hazards model with treatment group as a factor.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Secondary endpoints will include the following:

- Time from randomization to each component of the primary endpoint:
  - All-cause mortality
  - Any stroke
  - Any occurrence of major or life-threatening bleeding (as per VARC2 definition of bleeding)

- Time to death from cardiovascular causes
- Time to ischemic stroke
- Time to hemorrhagic stroke
- Arterial or venous thrombosis or embolism
- Rehospitalization related to WATCHMAN procedure or WATCHMAN device.
- Procedural costs related to the initial TAVR procedure and WATCHMAN device implantation.

Analysis of time-to-event endpoints for the components will be analyzed similarly to that of the primary endpoint, except there will be no testing of the non-inferiority hypothesis. Point estimates and 95% confidence intervals will be derived from a Cox proportional model with treatment group as a factor. Descriptive frequencies of the endpoints and Kaplan-Meier curves will be presented. P-values may be provided for descriptive purposes, but should not be considered informative. The frequency of procedure related complications, device/implant failure or systemic embolism will be summarized with descriptive statistics.

Costs directly related to the initial TAVR procedure and WATCHMAN device implantation will be collected.

9.4.4 SAMPLE SIZE

The WATCH-TAVR is a randomized, prospective multi-center event-driven non-inferiority study to determine the safety and efficacy of the WATCHMAN device in patients with non-valvular AF undergoing TAVR for aortic stenosis. The control group consists of patients undergoing TAVR who are on standard medical practice, with oral anticoagulation at the discretion of the treating physician. The treatment group will have the WATCHMAN implantation procedure performed simultaneously with TAVR. The primary endpoint is a composite of all-cause mortality, stroke, life-threatening or major bleeding. The objective of the study is to demonstrate non-inferiority of the TAVR plus WATCHMAN device compared to the TAVR only group.

Data from the PARTNER[1] trial, along with the SOURCE-XT[10] and FRANCE-2[11] registries show all-cause mortality rates in TAVR patients with AF vary from 19-30%, stroke rates from 6-10% and major/life-threatening bleeding from 17-22%. The PROTECT-AF trial for the WATCHMAN device in non-valvular atrial fibrillation patients reported a risk reduction of nearly 40% for the primary composite endpoint of stroke, systemic embolization or cardiovascular or unexplained death (RR 0.61, 95%CrI 0.42-1.07)[4].

The following assumptions were used to determine the sample size needed to assess the non-inferiority hypothesis for the composite primary endpoint of all-cause mortality, stroke or major or life-threatening bleeding:

- One-sided α =0.025
- Primary event rate in the control population (TAVR only) of 35% at one year
- Non-inferiority margin of 1.5
- Underlying hazard ratio of active to control is 1.0
- Power at least 80%
- Lost to follow-up rate 10%

Assuming level of significance (α) to be 0.05 (or α =0.025 one-sided) and aiming for a study power (1-β) of 80%, we estimate 191 primary events will be needed to rule out an upper limit of the one-sided 97.5% confidence interval of 1.5. Assuming an enrollment duration of 18 months, follow-up period of 24 months, and 10% drop out rate per annum, the minimum total sample size required is 350 (175per group).

10 ETHICS/PROTECTION OF HUMAN SUBJECTS

10.1 INSTITUTIONAL REVIEW BOARD

This protocol, the written informed consent form, and any materials presented to subjects shall be submitted to the IRB identified with this responsibility. Notification in writing of approval must come from the IRB chairman or secretary, to the investigator, either as a letter or as a copy of the appropriate section of the IRB meeting minutes where this protocol and associated informed consent form were discussed. The investigator will not participate in the decision. If the investigator is an IRB member, the written approval must indicate such non-participation in the voting session. The investigator will submit status reports to the IRB as required by the governing body. The IRB must be notified by the investigator in writing of the interruption and/or completion of the study; the investigator must promptly report to the IRB all changes in research (protocol amendments) and will not make such changes without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects. In cases where it is necessary to eliminate immediate hazards to subjects, the IRB must then be notified of the change as per local requirements. The investigator is required to maintain an accurate and complete records of all written correspondence to and received from the IRB and must agree to share all such documents and reports with the Sponsor.

10.2 INFORMED CONSENT PROCESS

10.2.1 CONSENT PROCEDURES AND DOCUMENTATION

Written informed consent will be obtained from all subjects (or their guardian or legally authorized representative) before any study-related procedures (including any pre-treatment procedures) are performed. The investigator(s)

has both ethical and legal responsibility to ensure that each subject (or their guardian or legally authorized representative) being considered for inclusion in this study is given a full explanation of the protocol. This shall be documented on a written informed consent form, which shall be approved by the same IRB responsible for approval of this protocol. Each informed consent form shall include the elements required by CRF21 part 50.25 and any applicable local regulations. The investigator agrees to obtain approval from the Sponsor of any written informed consent form used in the study, prior to submission to the IRB.

Once the appropriate essential information has been provided to the subject and fully explained by the investigators (or a qualified designee) and it is felt that the subject understands the implications of participating, the subject and the investigator (or designee) shall sign the IRB approved written informed consent form. The subject shall be given a copy of the signed informed consent form, and the original shall be filed appropriately, according to the institution. A second copy may be filed in the subject's medical record, if allowed by the institution.

10.3 PARTICIPANT AND DATA CONFIDENTIALITY

All information generated in this study must be considered highly confidential and must not be disclosed to any persons not directly concerned with the study without written prior permission from the Sponsor. However, authorized regulatory officials and Sponsor personnel will be allowed full access to the records.

Only unique subject numbers in eCRFs will identify subjects. Their full names may, however, be made known to a product regulatory agency or other authorized official if necessary.

11 DATA HANDLING AND RECORD KEEPING

11.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection will be with an electronic CRFs (eCRF). All users will be trained on the technical features of the EDC (Electronic Data Capture) as well as the content of the eCRF by qualified personnel prior to gaining access to the EDC. An User ID/Password will be granted after training. This ID is not to be shared amongst the study staff. The CRFs may be completed by clinical site personnel who have been authorized by the principal investigator and whose names are documented on the Signature Log,

Prior to the database being locked, the investigator or designee will review, approve, and sign/date each completed eCRF. This signature serves as attestation of the Investigator’s responsibility for ensuring that all data entered into the eCRF are complete, accurate, and authentic. After the end of the trial, a copy of the CRF data will be provided to the site. This copy will contain the final data, an audit trail of activity on the data, and any queries and answers that were posted for data clarification.

11.2 STUDY RECORDS RETENTION

All clinical sites will maintain study records for a minimum of two years after termination of the study. The investigator shall take responsibility for maintaining adequate and accurate hard copy source documents of all observations and data generated during this study, including any data clarification forms (DCFs) received from the Sponsor. Such documentation is subject to inspection by the Sponsor or its agents, and/or other regulatory agencies.

11.3 PROTOCOL DEVIATIONS

This study will be conducted as described in this protocol, except for an emergency situation in which the protection, safety, and well-being of the subject requires immediate intervention, based on the judgment of the investigator (or a responsible, appropriately trained professional designated by the investigator). In the event of a significant deviation from the protocol due to an emergency, accident, or mistake, the investigator or designee must contact the C5Research team within 5 days of the incident. This will allow an early joint decision regarding the subject's continuation in the study. The investigator and the Sponsor will document this decision. The IRB will be informed of all protocol changes by the investigator in accordance with the IRB established procedure.

11.4 PUBLICATION AND DATA SHARING POLICY

Publications addressing the WATCH-TAVR study will be managed by the study Steering Committee. The scientific validity and timing of publications will be evaluated in order to maximize the benefits derived from the publication of the worldwide clinical data of the study.

At the conclusion of the study, a multicenter abstract reporting the primary results will be prepared and presented at a major cardiovascular meeting. A multicenter publication will also be prepared for publication in a reputable scientific journal. We anticipate many secondary manuscripts with principal authorship drawn from members of the Steering Committee and Investigative sites. For purposes of timely abstract presentation and publication, such secondary publications will be delegated to the appropriate principal authors, and final analyses and manuscript review for all multicenter data will require the approval of the Steering Committee.

12 STUDY ADMINISTRATION

A Steering Committee consisting of academic experts who participated in the development of the protocol and/or will provide ongoing scientific and operational oversight to the study. This Committee will monitor progress of study enrollment, make recommendations to the Sponsors based on the Medical Monitor recommendations, and oversee the presentation and publication of the trial results. The membership, roles and responsibilities will be described in the SC Charter.

13 LITERATURE REFERENCES

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