The Evaluation of Thrombogenecity in Patients Undergoing WATCHMAN Left Atrial Appendage Closure (TARGET-WATCHMAN) Trial

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Device Name: The WATCHMAN™ Device

Sponsor: Boston Scientific, Inc.

Site of Investigation: Inova Heart and Vascular Institute at Inova Fairfax Hospital, Falls Church, VA

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PROTOCOL SYNOPSIS

Title: The evaluation of thrombogenecity in patients undergoing WATCHMAN left atrial appendage closure trial

Short Title: TARGET-WATCHMAN

Rationale: The results of this study will aid clinicians in better risk stratification of patients undergoing WATCHMAN left atrial appendage closure to prevent future thromboembolic and bleeding events. Additionally, the information will help guide the management of anticoagulation post-WATCHMAN implant, in particular the duration of anticoagulation and anti-platelet therapy.

Objectives
Primary: To identify biomarkers, parameters of thrombosis and platelet function to assist in identification of a thrombogenic phenotype in patients undergoing implantation of the WATCHMAN left atrial appendage closure device.

Secondary:
1. Determine differences in thrombogenicity among patients undergoing WATCHMAN left atrial appendage closure pre- and up to 1 year post- implant.
2. Identify blood biomarkers for predicting thrombo-embolic events and/or presence of LA thrombus detected on TEE performed 45 days, and at 1-year post-WATCHMAN implant.
3. Identify blood biomarkers for predicting major or clinically relevant non-major bleeding (CRNM) up to 1-year post-WATCHMAN implant.
5. Determine frequency of high on-treatment platelet reactivity and correlate to outcomes.
6. Determine frequency of low, medium, and high risk thrombogenic phenotype within the study population.
7. Identify changes in Galectin-3 and sST2 post-WATCHMAN implant and correlate to other biomarkers studied.

Study Type: Observational study design.

Study Design: Prospective, single center, observational study.

Study Methodology: This investigation will be conducted in subjects >18 years of age scheduled for WATCHMAN device implantation procedure. The study explores novel biomarkers to assess thrombogenicity in patients undergoing WATCHMAN left atrial appendage closure. Patients will undergo serial assessment of thrombogenicity and fibrosis over a twelve-month follow-up.

Patients: A total of 30 patients receiving WATCHMAN device implantation. It is expected that an additional 10 patients may be required to be enrolled to account for screen failures.

Statistical Methodology: Pearsons' correlation coefficient, univariate and multivariate logistic regression models, ROC curve analysis. Statistical calculations will be carried out using SAS® for Windows, version 9.3 or later (Cary, NC).

1 INTRODUCTION

1.1 Specific Aims

- To quantify and characterize specific biomarkers of thrombogenicity in patients undergoing WATCHMAN implant, both pre- and post-procedure.
- To identify variations in thrombogenic phenotypes which play a role in the varied incidence of thromboembolic complications amongst patients undergoing percutaneous left atrial appendage closure with the WATCHMAN implant
- Obtain pilot data for future translational trials aimed at personalizing antithrombotic therapy (duration of anticoagulation and anti-platelet therapy) by thrombogenic phenotype in WATCHMAN patients.

1.2 Hypothesis

We hypothesize that serial evaluation of (a) platelet activation and aggregation, (b) intrinsic thrombogenicity measured by thrombelastography, and (c) selected biomarkers will provide the "blueprint" of individual hemostasis to precisely characterize patients who have thrombotic or bleeding tendencies. The latter will facilitate future efforts to personalize antithrombotic therapy regimens during and following WATCHMAN implant.

1.3 Background and Significance

Atrial fibrillation (AF) is associated with an increased risk of stroke and thromboembolism.[1] Anticoagulation, with either warfarin or the novel anticoagulants (NOACs) is recommended for patients at increased risk of stroke, based on the CHA2DS2-VASc scoring system. However, treatment with these agents is not without its limitations and may be associated with serious side effects, of which major gastrointestinal bleeding and hemorrhagic stroke are the most devastating. Non-pharmacologic strategies for stroke prevention in patients with atrial fibrillation exist. Percutaneous left atrial appendage closure with the WATCHMAN device is an FDA approved modality, and exists as an option for stroke reduction in patients with atrial fibrillation, deemed to be at high risk for long term anticoagulation.

Current guidelines for WATCHMAN implant require that a patient must be treated with at least 45 days of warfarin post WATCHMAN implant and then six months of a combination of aspirin and clopidogrel. This duration of therapy is based on the data from two large clinical trials (Protect AF and Prevail) involving WATCHMAN implant and several CAP registries.[2-5]

No data exists on whether there are differences in markers of thrombogenicity among patients undergoing WATCHMAN implant, and whether those differences could be used to guide the management of anticoagulation and anti-platelet therapy pre- and post-WATCHMAN implant. The purpose of this study will be to quantify and characterize specific biomarkers of thrombogenicity in patients undergoing WATCHMAN implant, both pre- and post-procedure. In addition, we seek to find variations in thrombogenic phenotypes

which play a role in the varied incidence of thromboembolic complications amongst patients undergoing percutaneous left atrial appendage closure with the WATCHMAN implant. Furthermore, the individual thrombogenic phenotype may be used to guide anticoagulation in these patients, more specifically the duration of anticoagulation and anti-platelet therapy. This will be established by utilizing biomarkers assessed by thrombelastography (TEG), platelet aggregation, CAT assay, fibrinogen levels, urinary thromboxane, D-dimer, CRP and PAI-1. We hypothesize that by utilizing these assays, we can accurately identify a thrombogenic phenotype in patients undergoing WATCHMAN implant for left atrial appendage closure and help predict and manage the risk of subsequent thrombotic complications. The proteins soluble ST2 (sST2) and galectin-3 are currently gaining mounting interest as candidate biomarkers in cardiac disease which have been utilized to measure acute inflammation to chronic inflammation and tissue fibrinogenisis. In this pilot study, we will assess changes in Galectin-3 and sST2 post-WATCHMAN implant and correlate to other biomarkers studied.

2 POST-IMPLANTATION CARE

The device implantation procedure is performed in a standard fashion per device implant protocol in the cardiac catheterization laboratory. Device selection is based on accurate left atrial appendage measurements obtained in multiple angles. The device is permeable to blood thus patients require post-procedure warfarin therapy for 45 days on a dose assuring a therapeutic INR level and ASA 81mg. A transesophageal echocardiography (TEE) is performed for device assessment 45 days post-procedure after which a decision is made to discontinue warfarin. If the TEE shows no leak > 5mm around the device and no left atrial (LA) thrombus, warfarin is discontinued and the patient is treated with clopidogrel 75 mg and aspirin 325mg for up to 6 months, after which the clopidogrel is discontinued and aspirin 162-325mg thereafter. If the follow-up TEE at 45 days shows a leak > 5mm around the device or a LA thrombus is noted, the patient will need to remain on warfarin for another 6 months (or upon resolution of thrombus), and another TEE performed thereafter.

If the TEE performed at 45 days shows that the opening of the LAA is not adequately closed, another TEE may be scheduled at around 6 months to re-evaluate whether adequate closer of the LAA has occurred. At about 12 months after the WATCHMAN implant, another TEE is performed to check on the device and make sure that the LAA is still closed.

3 STUDY DESIGN AND SUBJECT SELECTION

3.1 Study Type

This is an observational study that will be conducted in subjects scheduled for the WATCHMAN device implantation. The laboratory assessments (see section 1.1) will be performed at the baseline (pre-procedure), post-implantation, 45 days, 6 months, and 12 months post-procedure (see table 1).

3.2 Duration of Study

Subject participation will be for 12 months after obtaining consent.

3.3 Number of Subjects

Thirty patients scheduled for WATCHMAN device implantation.

3.4 Study Population

3.4.1 Population Characteristics

3.4.1.1 Gender and racial and ethnic origin of subjects

The study's intended population is inclusive of both genders (males and females), and all racial and ethnic groups and subgroups.

3.4.1.2 Age of subjects

Subject enrollment will be comprised of subjects >18 years of age.

3.4.2 Vulnerable Population

Children, pregnant women, institutionalized persons, and persons with decisional incapacity will be not be enrolled in this study.

3.5 Recruitment

Recruitment will occur at the Inova Heart and Vascular Institute. The expected length of the recruitment period is 16 months. The average number of WATCHMAN left atrial appendage closure procedures performed at INOVA is approximated to be 60 per year. If the study conduct (e.g. recruitment rate; drop-out rate; data quality; protocol compliance) does not suggest a proper completion of the trial within the reasonable time frame as agreed upon, the recruitment period may be extended to reach the desired sample size.

3.6 Inclusion Criteria

- Subject indicated and scheduled for WATCHMAN device implantation at IHVI.
- Subject may be of either sex and of any race, and must be >18 years of age.
- Subject must be willing and able to give appropriate informed consent.
- The subject is able to read and has signed and dated the informed consent document including authorization permitting release of personal health information approved by the investigator's Institutional Review Board (IRB).

3.7 Exclusion Criteria

Subjects will be excluded from entry if ANY of the criteria listed below are met:

- Subjects with contraindications for WATCHMAN device implantation
  - Intracardiac thrombus is visualized by echocardiographic imaging
  - An atrial septal defect repair or closure device or a patent foramen ovale repair or closure device is present
  - The LAA anatomy will not accommodate a device
  - Any of the customary contraindications for other percutaneous catheterization procedures (e.g., patient size too small to accommodate TEE probe or required catheters) or conditions (e.g., active infection, bleeding disorder) are present.
  - There are contraindications to the use of warfarin, aspirin, or clopidogrel
  - The patient has a known hypersensitivity to any portion of the device material or the individual components such that the use of the WATCHMAN Device is contraindicated
- Ligated or oversewn left atrium
- Concurrent participation in any investigational study

- Subject likely to not be available to complete all protocol-required study visits or procedures, to the best of the subject's and investigator's knowledge
- History or evidence of any other clinically significant disorder, condition, or disease other than those outlined above that, in the opinion of the investigator, may compromise the ability of the subject to give written informed consent, would pose a risk to subject safety or interfere with the study evaluation, procedures, or completion.

4 STUDY METHODS

4.1 Laboratory Measurements

Phlebotomy sites will be carefully chosen to minimize risk and platelet activation. In addition, blood from the left atrium via transeptal sheath will be collected during the procedure to compare clotting at the site of implant and the periphery. After discarding the first 2-3mL of free flowing blood, the blood collection tubes will be filled to capacity and gently inverted 3 to 5 times to ensure complete mixing of the anticoagulant. At each visit blood (total=approximately 17 ml each visit) will be collected in two 3.2% trisodium citrate tubes (light transmittance aggregometry and thrombelastography), one CTAD tube containing buffered citrate solution, theophylline, adenosine and dipyridamole (activation markers) and one serum separator tube (lipid and biomarker measurements).

- *Platelet Aggregation by Light Transmittance Aggregometry* (LTA) (Chronolog) Platelet aggregation will be assessed in platelet-rich plasma using a Chronolog Lumi-Aggregometer (model 490-4D) with the AggroLink software package after stimulation with 5 and 20 μM ADP, 2mM AA, and 4ug/ml collagen.[6]

- *TEG6S with citrated multi-channel cartridge*
  The TEG6s instrument is a microfluidic fully automated cartridge-based device. The standard hemostasis assay cartridge (Citrated Multi-Channel, CMC) uses a citrated blood sample that is mixed with dried reagents within each of the 4 channels, each with calcium chloride (to reverse the sodium citrate) and: (1) kaolin, (2) kaolin+ tissue factor activated (RapidTEG), (3) kaolin + heparinase, and (4) kaolin + abciximab (functional fibrinogen).[7]

- *Thrombogram (CAT assay)*: Uses a slow fluorogenic thrombin substrate and continuous comparison to a simultaneously run calibrator, thrombin generation can be monitored automatically, on line, in clotting PPP or PRP at a throughput of up to 100 samples per hour. The resulting "Thrombogram" in PPP measure patients with hypo- or hypercoagulable phenotypes.[8]

- *Urinary 11-dehydrothromboxane B2 (UTBx):* Measures endogenous platelet activation.[9]

- *Soluble biomarkers* (fibrinogen, d-dimer, hsCRP, and PAI) to indicate thrombogenicity, oxidative stress, endothelial dysfunction, and inflammation.

- *Markers of fibrosis:* sST2 and Galectin-3 markers measure maladaptive response to tissue fibrosis.[10]

4.2 Primary and Secondary Objectives

4.2.1 Primary Objective

To identify biomarkers, parameters of thrombosis and platelet function to assist in identification of a thrombogenic phenotype in patients undergoing implantation of the WATCHMAN left atrial appendage closure device.

4.2.2 Secondary Objectives

- Identify blood biomarkers for predicting thrombo-embolic events and/or presence of LA thrombus detected on TEE performed 45 days, and at 1-year post-WATCHMAN implant.
- Determine differences in thrombogenicity among patients undergoing WATCHMAN left atrial appendage closure pre- and up to 1 year post- implant.
- Identify blood biomarkers for predicting thrombo-embolic events and/or presence of LA thrombus detected on TEE performed 45 days, and at 1-year post-WATCHMAN implant.
- Identify blood biomarkers for predicting major or clinically relevant non-major bleeding (CRNM) up to 1-year post-WATCHMAN implant.
- Determine frequency of high on-treatment platelet reactivity and correlate to outcomes.
- Determine frequency of low, medium, and high risk thrombogenic phenotype within the study population.
- Identify changes in Galectin-3 and sST2 post-WATCHMAN implant and correlate to other biomarkers studied.

4.2.3 Clinical Endpoints

- Thrombo-embolic events (Death, Stroke, and MI) and/or presence of LA thrombus detected on TEE.
- Bleeding using Academic Research Consortium (BARC) definition.

4.3 Informed Consent

The research staff will meet with the participant to discuss the study, explain the goals, risks/benefits, answer questions, while allowing adequate time and privacy for decision making, and then obtaining a signed consent document. Patients incapable of providing consent due to a medical situation will not be approached for study participation. No study related procedures may commence without a signed consent form.

5 STATISTICAL CONSIDERATIONS/DATA ANALYSIS

5.1 Statistical Calculations

No data exists on whether there are differences in markers of thrombogenicity among patients undergoing WATCHMAN implant, and if those differences could be used to guide the management of anticoagulation and anti-platelet therapy pre- and post-WATCHMAN implant. Similar pharmacodynamic studies conducted in device trials (Coronary Stent, TAVR) have typically enrolled 30- 75 patients to determine serial changes in thrombogenicity and in biomarkers after implant. No similar size analysis has been

performed with WATCHMAN patients. As such a reasonable calculation of a sample size based on the accepted error rate is currently not feasible.

5.2 Statistical Analysis

Categorical variables will be expressed as n (%). Continuous variables with normal distributions will be reported as mean [standard deviation (SD)], while variables not having a normal distribution were reported as median (interquartile). Wilcoxon signed rank tests or paired t-tests will be performed to test differences in lab values before and after implant. Correlation analysis will be performed by Pearson's correlation coefficient. Univariate and multivariate logistic regression models will be used to determine predictors of clinical endpoints. The predictive cut-point values of platelet function tests or rate of fibrinolysis will be assessed by ROC curve analysis. Statistical calculations will be carried out using SAS® for Windows, version 9.3 or later (Cary, NC).

5.3 Future Experiments:

Our initial pilot study will allow for adjustments to our experimental methodology and will provide insights into the potential value of this analysis for determining an individual WATCHMAN recipient's degree of antithrombotic therapy. If our pilot data is interesting we then plan to expand our analysis to a consortium of WATCHMAN research centers. A larger cohort will allow validation of our initial findings. Future experiments will then focus on titration of anticoagulation and antiplatelet therapy to reduce the risk of bleeding and thrombotic complications. In addition, the individual thrombogenic phenotype may be used to guide anticoagulation in these patients, more specifically the duration of anticoagulation and anti-platelet therapy. To facilitate these and future studies, we plan to submit our pilot data generated from this grant as part of future grant applications.

6 VISIT SCHEDULE AND ASSESSMENTS

Informed consent will be obtained from subjects meeting the inclusion criteria and none of the exclusion criteria before the initiation of any study-specific procedures. The study comprises of 4 periods: (1) Procedural (pre and post WATCHMAN implantation, (2) 45 days post-procedure, (3) 6 months post-procedure, and (4) 12 months post-procedure. Required assessments for each study visit are listed in Table 1. Subjects should be seen for visits on the designated day or according to the allowed window period (see Table 1).

Each clinic visit includes laboratory measurements, safety assessment, and health and concomitant medication review. A complete physical exam is required for visit 1 (baseline).

- **Laboratory measurements**

Laboratory measurements (see section 4.1) will be obtained at baseline (prior to device implantation procedure), immediately post-procedure, 45 days, 6 months, and 12 months post-procedure. Laboratory measurements needed at baseline and immediately post-procedure will be done while the subject is on the pre-op area, angiography suite, and/or recovery area. The study will require clinic visits during the required laboratory measurements for 45 days, 6 months, and 12 month post-procedure.

- **Health and concomitant medication review**

During the follow-up clinic visits, changes in participant's medical condition (any new diagnosis, etc.) and concomitant medications should be updated. Note that only anticoagulation and anti-platelet therapies will be collected. Adverse events will be reported, side effects and symptoms assessed.

- **Physical Exam**

A physical exam will be conducted by the investigator during the screening period after obtaining consent to evaluate the general status of the subject and to further elucidate patient symptoms, risk factors, or concerns that may increase the subject's risk for adverse events.

- **Safety assessments**

Safety assessments will consist of monitoring and recording of serious adverse events (see section 10). The occurrence of adverse events should be sought by non-directive questioning of the subject at each visit during the study. AEs may also be detected when these are volunteered by the subject during or between visits or through physical examination, laboratory test, or other assessments. For the purpose of this study, only (a) thromboembolic and (b) bleeding events, and (c) serious adverse events (SAEs) directly related to study procedures, or (d) SAEs not previously reported to a left atrial appendage closure device or implantation (see device package insert) with potential relatedness to the WATCHMAN device will be collected and reported (see section 10).

Additional assessments required to ensure safety of subjects should be administered as deemed necessary by the investigator on a case by case basis.

Table 1
Schedule of Events

	V1		**V2[5]**	**V3[5]**	**V4[5]**
	Pre-procedure	**Immediately post-procedure**	**45 days post-procedure (± 10 days)**	**6 months post-procedure (±1 month)**	**12 months post-procedure (± 1-month)**
Informed Consent	X				
Inclusion/Exclusion Criteria	X				
Medical History	X				
Review Prior/Concomitant Medications[1]	X	X	X	X	X
Physical Examination	X				
Height, weight, Blood pressure, heart rate measurements	X				
TEE[2]	X		X		X
Laboratory Measurements: TEG6S and platelet aggregation	X	X	X	X	X

	V1		V2[5]	V3[5]	V4[5]
	Pre-procedure	**Immediately post-procedure**	**45 days post-procedure (± 10 days)**	**6 months post-procedure (±1 month)**	**12 months post-procedure (± 1-month)**
Laboratory Measurements: Thrombogram (CAT assay), urinary thromboxane,biomarkers, markers of fibrosis	X	X[6]	X	X	X[3]
Adverse events[4]	X	X	X	X	X

[1] Anticoagulation and anti-platelet therapies only
[2] Standard of care procedure
[3] Thrombogram, urinary thromboxane, biomarkers, and markers of fibrosis obtained only if subject have reports of thromboembolic events post-implantation
[4]Only thromboembolic and bleeding events, SAEs not previously reported to WATCHMAN device or implantation procedure (see device package insert) with potential relatedness to the WATCHMAN device/implantation procedure and SAEs directly related to study procedures will be collected
[5]The 45 days, 6 months, and 12 month visits post-procedure coincide with recommended standard of care follow-up visits post-WATCHMAN implantation procedure.
[6]Urinary thromboxane will not be performed at post-procedure time point

6.1 Timing of Assessments

6.1.1 Visit 1: Procedural Day

6.1.1.1 Pre-procedure

The site principal investigator is responsible for reviewing and confirming that the subject signed and dated the ICF prior to any study-related procedures. Additionally, the site PI is responsible for reviewing and confirming that each subject met all inclusion and none of the exclusion criteria prior to WATCHMAN device placement.

The following tests and procedures are performed prior to device implantation:

- Subject demographic and baseline characteristics.
  - Demographic data to be collected on all subjects include: date of birth, age, sex, race, and ethnicity.
- Past medical history and co-morbidities
- Height and weight blood pressure and heart rate prior to procedure
- Concomitant medication review. Only anticoagulants and anti-platelet medications will be recorded in source documents (CRFs).
- Perform complete physical examination.
- Laboratory measurements for TEG 6S, platelet aggregation, thrombogram, urinary thromboxane, biomarkers, and markers of fibrosis will be obtained prior to implantation procedure.

6.1.1.2 Immediately post-procedure

The procedure will be completed according to operating physician's standard practice in an angiography suite. The following tests and procedures are performed immediately after device implantation:

- Laboratory measurements for TEG 6S, platelet aggregation, thrombogram, , biomarkers, and markers of fibrosis will be obtained immediately post-procedure.
- Concomitant medication: all anticoagulant and antiplatelet medications will be collected.
- Safety assessment (see section 10)

6.1.2 Treatment Failures

Failure to implant the WATCHMAN device will be recorded on the paper CRF as a treatment failure. In the event of a failure to implant the device, each site will follow their standard of care procedures and/or commercially available products to ensure safety of the subject. The reason for unsuccessful implantation (e.g. product malfunction) will be documented. Subjects will be exited from the study after failure and no other study-related procedures are required.

6.1.3 Follow-Up Assessments

Subjects are followed until 12 months after device implantation. Subjects will have follow-up visits at 45 days, 6 months, and 12 months post-procedure. These visits may coincide with standard of care follow-up visits post WATCHMAN device implantation procedure.

The following assessments will be performed at each in-person follow-up visit

- Laboratory measurements (see table 1 for laboratory measurements required for each follow-up visit) will be obtained.
- Adverse event monitoring (see section 10).
- Health and medication review. Anticoagulant and antiplatelet therapies will be collected.

6.2 Lost to Follow-Up and Subject Withdrawal

All subjects should be encouraged to return for protocol-required clinic visits for evaluation during the study follow-up period. If a subject is unable to return for a clinic visit, all attempts should be documented in the source documents. If the subject does not respond to 3 telephone calls, then the Investigator must send the subject a certified letter. Only after failing to contact the subject using the methods above will the subject be considered a lost to follow-up.

If the subject withdraws from the study, the reason for withdrawal must be documented. Possible reasons for early withdrawal may include but are not limited to the following:

- Subject decides to withdraw from the study. Documentation of subject's decision to withdraw is documented in the CRFs.
- The Investigator may choose to withdraw a subject from the study if there are safety concerns.
- Death

7 DATA MANAGEMENT

7.1 Data Storage and Management

Designated study site staff will record data required by the protocol into the CRFs and enter it into the electronic database. Authorized research staff will review the CRFs for completeness

and accuracy and make any necessary corrections to the data entered into the electronic database. Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Each subject screened and enrolled will be assigned a subject identification number (ID) and a list of subjects with their corresponding subject ID will be maintained separately from collected data. Physical CRFs will be stored in the research site in a locked office and electronic subject data will be locked in a password protected file on a secure internet server, accessed only by authorized research staff.

7.2 Records Retention

The Investigator will maintain the records of final CRFs (CDROM copies), worksheets, paper source documents, and all other study-specific documentation in accordance with ICH Guidelines. Essential documents should be retained until at least two (2) years after the investigation is formally discontinued.

7.3 Confidentiality

Subject information will be kept confidential as according to HIPAA requirements. Subject data will be stored and managed as outlined in section 7.1. All data records will be stored on site until 2 years after the investigation is formally discontinued. Paper records will be shredded and recycled. Records stored on a computer hard drive will be erased using a commercial software application designed to remove all data from the storage device.

7.4 Oversight

The principal investigator holds ultimate responsibility for the oversight and execution of the data and safety monitoring plan. This research site will be fully committed in the ongoing review and refinement of the trial's processes to assure subject safety, data validity and integrity, and regulatory compliance.

8 HUMAN SUBJECTS PROTECTION (RISKS, BENEFITS, AND ALTERNATIVES)

8.1 Risks

8.1.2 Potential Loss of Privacy

Protected health information (PHI) will be collected during the study. The risk for breach of confidentiality and privacy will be minimized by shielding the subjects unlinking his or her identity from his or her personal health information.

8.1.3 Potential Adverse Events

For the purpose of this study (see section 10), only thromboembolic and bleeding events, SAEs related to study procedures (e.g. nerve damage directly related to blood draw), and SAEs not previously reported by device manufacturer with potential relatedness to the device or implantation procedure (see package insert) will be collected and reported. SAEs should be treated appropriately and managed as according to standard of care.

8.1.4 Economic risk

Subjects in the study may lose time at work or home and spend more time in the research site more than usual. Visit schedules will be made flexible for subjects (as allowed by protocol).

8.2 Benefits and Alternatives

There are no direct benefits to the patient. Participation in the study is entirely voluntary. The alternative is not to participate in the trial.

9 SUBJECT COMPENSATION

9.1 Costs

This is an investigator-initiated study sponsored by Boston Scientific, Inc. The subject or their insurance company will not be billed for study-specific procedures (e.g. laboratory measurements for TEG 6S, etc.). All study-specific tests and procedures will be paid for by the research site.

9.2 Payment

Subjects may receive up to $75 for their participation in this study. Subjects will be reimbursed $25 for each follow-up visit at the study site to cover their expenses associated with those visits.

10 ADVERSE EVENT REPORTING

10.1 AE Reporting

For the purpose of this study, only the following adverse events will be collected and reported:

-Thromboembolic events
-Bleeding events using BARC definitions (see section 10.5)
-SAEs related to study procedures (i.e. SAEs directly related to phlebotomy procedure)
-SAEs not previously reported by device manufacturer with potential relatedness to the device or implant procedure. For serious adverse events not previously documented in study device's Package Insert (new occurrence) and are thought to be related to the study device or implant procedure, the investigator may urgently require further information from the investigator for Health Authority reporting. Boston Scientific Corporation or designee may need to issue an IDE Safety Report (Investigator Notification) to inform all investigators involved in any study with the same device that this SAE has been reported.

10.2 Adverse Events Treatment

All AEs should be treated appropriately and managed as according to standard of care. The action taken to treat the AE should be recorded on the AE CRF (see section 10.3). Assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, relationship to the study procedures (if applicable), the interventions required to treat it, and the outcome.

10.3 Adverse Event Reporting

The principal investigator has the primary responsibility for SAE identification, documentation, grading, and assignment of attribution to the study intervention. Note that only SAEs related to study procedures (e.g. arterial puncture, etc.), clinical endpoints (see section 4.2.3), and SAEs not previously reported by manufacturer with potential relatedness to device or implantation procedure will be collected and reported. SAEs must be recorded in the AE CRF with the following information:

-AE term
-The intensity grade (CTCAE v4.03 grading)

-The relationship to study procedure
-Attribution
-Duration
-Occurrence (known risks for study procedure-expected, unexpected)
-Other contributing causes
-Actions in response to event
-Outcome
-Criteria for SAE

10.4 AE Grading Scale

The descriptions and grading scales found in NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be used for AE reporting. Each AE term is associated with a 5-point severity scale.

10.5 Bleeding Definitions

Bleeding events will be documented using the Bleeding Academic Research Consortium (BARC) standard definitions described below (excluding Type 4) .[11]

Bleeding Academic Research Consortium Definition for Bleeding
Type 0: No bleeding
Type 1: Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a health-care professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a health-care professional.
Type 2: Any overt, actionable sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: • requiring nonsurgical, medical intervention by a health-care professional, • leading to hospitalization or increased level of care, or • prompting evaluation
Type 3: Type 3a: • Overt bleeding plus hemoglobin drop of 3 to < 5 g/dL* (provided hemoglobin drop is related to bleed) • Any transfusion with overt bleeding Type 3b: • Overt bleeding plus hemoglobin drop ≥5 g/dL* (provided hemoglobin drop is related to bleed), • Cardiac tamponade, • Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid), • Bleeding requiring intravenous vasoactive agents Type 3c: • Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation,

does include intraspinal), • Subcategories confirmed by autopsy or imaging or lumbar puncture, • Intraocular bleed compromising vision.
Type 4: (not required for this trial) • CABG-related bleeding, • Perioperative intracranial bleeding within 48 h, • Reoperation after closure of sternotomy for the purpose of controlling bleeding • Transfusion of ≥ 5 U whole blood or packed red blood cells within a 48-h period, • Chest tube output more than or equal to 2L within a 24-h period
Type 5: Fatal bleeding Type 5a: • Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious Type 5b: • Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

10.6 Protocol Deviations and Violations

The principal investigator will not deviate from the protocol without obtaining approval from the IRB or Ethics Committee and the sponsor. Protocol deviations that occur will be reported to the Inova IRB at the time of continuing review. Protocol violations that affect the subject's rights and safety, and/or affects study integrity will be reported to the Inova IRB within 10 working days of event knowledge.

11 FUNDING

This is an investigator-initiated study sponsored by Boston Scientific, Inc. There is no investigational product involved. Treatment received by the subject will be as according to main provider's discretion as according to standard of care.

12 CONFLICTS OF INTEREST

The investigators declare no conflicts of interest linked to this study.

13 FACILITIES AND EQUIPMENT

The research site is equipped with its own laboratory equipment, which includes state of the art technologies for platelet assays, centrifuges, refrigerators, and freezers for study specimen processing and storage. For outpatient visits, subjects will be seen in the site's outpatient clinic room equipped with supplies and equipment for necessary for subject assessment.

14 OUTSIDE CONSULTANTS/COLLABORATORS

There are no outside consultants/collaborators participating.

15 CONTRACTURAL AGREEMENTS

There are no outside consultants/collaborators participating.

16 REFERENCES

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