PROTECTED TAVR: Stroke PROTECTion with SEntinel During Transcatheter Aortic Valve Replacement

PROTECTED TAVR

S2453

CLINICAL INVESTIGATION PLAN

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Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
A	18-Oct-2019	92120219 Rev/Ver C	–	Not applicable.	–
B	06-Nov-2019	92120219 Rev/Ver C	Section 2, Synopsis, Planned Number of Centers	Up to 100 study centers in North America, ~~Western~~ Europe, and…	Allow for additional centers.
			Section 2, Synopsis, Additional Measurements	This section describes additional measurements to be performed… • Health status as evaluated by EQ-5D Quality of Life questionnaire at baseline	Health economics analysis
			Section 6.2.2 Additional Measurements	The additional measurements shown below… • Health status as evaluated by EQ-5D Quality of Life questionnaire at baseline	
			Section 7.3, Justification for the Study Design	In order to support the stated objectives… at up to 100 centers in North America, ~~Western~~ Europe, and…	Allow for additional centers.
			Section 10.1, Data Collection	Figure 10.1-1: Updated figure to include EQ-5D at baseline Table 10.1-1: Added table row to collect the EQ-5D Quality of Life questionnaire at baseline Added footnote j: EQ-5D Quality of Life questionnaire at baseline	Health economics analysis
			Section 10.4, Baseline Assessments	The following assessments… • Quality of Life Survey (EQ-5D[27, 28]) should be administered within 30 days prior to the procedure	
			Section 11.3.2 Interim Analyses	One formal interim analysis is planned… Additional analyses not defined in the protocol may also be conducted for regulatory agency review.	Allow for additional regulatory agency analyses.

Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
			Section 12. Health Economics Outcomes	A formal health economics… healthcare resource utilization ~~associated with periprocedural stroke subjects with~~ through discharge (with a maximum of ~~up to~~ 30 days if the subject is hospitalized longer than 30 days) ~~of follow up~~ for both the Test and Control groups. Medical billing information (e.g., UB-04 billing claim form) through the TAVR index hospitalization may be collected at centers in the United States for health economics analyses.	Health economics analysis
			Section 24, Bibliography	Add 2 new references for EQ-5D (27 and 28)	

2. Protocol Synopsis

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Study Objective	The objective of this study is to demonstrate that use of the Sentinel® Cerebral Protection System significantly reduces the risk of peri-procedural stroke (≤72 hours) after transcatheter aortic valve replacement (TAVR).
Indications for Use	The Sentinel® Cerebral Protection System is indicated for use as a cerebral protection device to capture and remove embolic material while performing transcatheter aortic valve procedures in order to reduce ischemic injury to the brain peri-procedurally.
Commercial Device Applied as Standard of Care (Test Cohort)	Commercially available Sentinel® Cerebral Protection System (Sentinel; Boston Scientific Corporation, Marlborough, MA, USA) ***Note 1*:** In the Test cohort, subjects will undergo TAVR with Sentinel. The participating investigator must be a trained, experienced Sentinel user.
Control Applied as Standard of Care (Control Cohort)	Subjects in the Control cohort will undergo TAVR with no cerebral protection device.
Study Design	PROTECTED TAVR is a prospective, post-market, multicenter randomized controlled trial (RCT) evaluating use of the Sentinel Cerebral Protection System in subjects with aortic valve stenosis who are treated with a commercially available TAVR device. Subjects to be treated via a transfemoral approach will be randomized 1:1 into a Test cohort using the commercially available Sentinel or a Control cohort with no cerebral protection system. A subject who provides an Informed Consent Form (ICF) signed by the subject or the subject's legally authorized representative is considered enrolled in the study upon randomization, which will occur at the index procedure prior to procedural puncture/incision. enrolled subjects will be followed through 72 hours or hospital discharge, whichever comes first (see Additional Measurements below for information regarding subjects with suspected stroke). An overview of the study design is shown below. Every subject must be deemed treatable with the Sentinel device (have suitable anatomy

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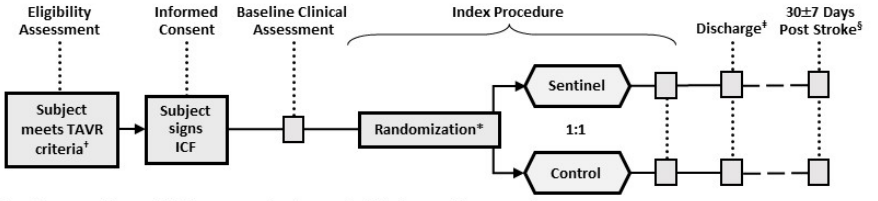
	per the Sentinel Instructions For Use [IFU]). All eligible subjects (see below) should be approached for participation in the trial.  † Subject must have suitable anatomy for the Sentinel device per the Instructions For Use. * Subjects who provide informed consent are considered enrolled upon randomization, which will occur at the index procedure prior to procedural puncture/incision. ‡ ≤72 hours or discharge, whichever comes first § For subjects diagnosed with a stroke the study duration will be through 30±7 days post stroke. **PROTECTED TAVR Study Design Overview** An initial enrollment of up to 3000 randomized subjects is planned. There will be 1 planned formal interim analysis performed on the first 70% of enrolled subjects by the Independent Safety and Statistical Monitor. The study will be stopped if a significant difference in favor of the test arm is observed. If the study cannot be stopped after the interim analysis, sample size re-estimation may be performed as discussed below (see Statistical Methods). A final analysis will be performed on all enrolled subjects if the trial is not stopped after the interim analysis. The PROTECTED TAVR study will be conducted in accordance with 21 CFR Parts 11, 50, and 54; the relevant parts of the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practices (GCP); the International Standard ISO 14155 Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice; ethical principles that have their origins in the Declaration of Helsinki; and pertinent individual country/state/local laws and regulations. The study shall not begin until the required approval/favorable opinion from the Institutional Review Board (IRB)/Independent Ethics Committee (IEC)/Human Research Ethics Committee (HREC) and/or regulatory authority has been obtained, if appropriate.
Planned Number of Subjects	An initial enrollment of up to 3000 randomized subjects is planned. If sample size re-estimation is needed (see Statistical Methods below), the planned maximum enrollment will be up to 6000 randomized subjects.

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Planned Number of Centers	Up to 100 study centers in North America, Europe, and Australia will participate in PROTECTED TAVR.
Primary Endpoint	The primary endpoint is all stroke (hemorrhagic, ischemic, or undetermined status; disabling or nondisabling) through 72 hours post TAVR procedure or discharge (whichever comes first), as adjudicated by an independent Clinical Events Committee (CEC) and using Neurologic Academic Research Consortium (NeuroARC[a]) definitions. a: Lansky AJ, et al. *J Am Coll Cardiol*. 2017;69:679–691
Additional Measurements	This section describes additional measurements[a,b] to be performed in the PROTECTED TAVR study. Measurements will be assessed through 72 hours post TAVR procedure or hospital discharge (whichever comes first). Mortality (cardiovascular and non-cardiovascular), neurological endpoints (stroke, transient ischemic attack, and delirium), acute kidney injury, and Sentinel access site major vascular complications will be adjudicated by an independent CEC. • All-cause mortality (cardiovascular and non-cardiovascular[b]) • Neurological endpoints[a] (see ***Note 2*** below) o Stroke (disabling and non-disabling) o Transient ischemic attack (TIA) o Delirium • Safety composite of all-cause mortality and all stroke • Neurological and neurocognitive status as determined by the following assessments[a] (see ***Note 2*** below): o Neurological physical examination o Modified Rankin Scale (mRS) score o National Institutes of Health Stroke Scale (NIHSS) o Confusion Assessment Method for Intensive Care Unit Patients (CAM-ICU) o Montreal Cognitive Assessment (MoCA) • Neurological complications composite of all stroke, TIA, and delirium

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	• Acute kidney injury based on the AKIN System Stage 3 (including renal replacement therapy) and Stage 2[b] • Sentinel access site vascular complications related to the procedure (major and minor)[c] • Sentinel system acute delivery and retrieval (categorized as successful deployment of both filters, 1 filter, or no filter and retrieval of the system) • Health status as evaluated by EQ-5D Quality of Life questionnaire at baseline ***Note 2*:** The neurological physical examination must be carried out by a neurology professional (board certified/board eligible neurologist, neurology fellow, neurology physician assistant, or neurology nurse practitioner). The NIHSS, mRS, and MoCA must be performed by certified personnel. The CAM-ICU must be performed by personnel with appropriate training. In all subjects where stroke is suspected, a formal neurology/stroke consult should be obtained, and the subject should be further assessed and treated per standard of care. In subjects diagnosed with post-procedural stroke, mRS must also be administered 30±7 days following the stroke; the simplified mRS questionnaire[d] may be used for this follow-up assessment. a: Lansky AJ, et al. *J Am Coll Cardiol*. 2017;69:679–691 b: Mehta RL, et al. *Crit Care.* 2007;11:R31 c: Kappetein AP, et al. *J Am Coll Cardiol*. 2012;60:1438–1454 Leon M, et al. *J Am Coll Cardiol*. 2011;57:253–269 d: Bruno A, et al. *Stroke* 2011;42:2276–2279
Method of Assigning Subjects to Treatment	Subjects to be treated with a commercially available TAVR device will be randomized 1:1 at the index procedure prior to procedural puncture/incision into a Test cohort using the commercially available Sentinel or a Control cohort with no cerebral protection system. Randomization will be stratified by center, by operative risk and by intended TAVR valve type.
Follow-up Schedule	All subjects will be assessed at baseline, peri- and post-procedure, and through 72 hours or discharge (whichever comes first).
Study Duration	Subjects will be followed through 72 hours or hospital discharge post TAVR procedure (whichever comes first).

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	The planned initial enrollment of 3000 subjects is expected to be completed in approximately 30 months; therefore, the study duration is estimated to be less than 32 months (see ***Note 3*** below). Note that enrollment may be extended based on the planned interim analysis (see Statistical Methods below).
Participant Duration	The study duration for each subject is expected to be through 72 hours or hospital discharge post TAVR procedure (whichever comes first). ***Note 3*:** In subjects diagnosed with a stroke, mRS must be administered at 30±7 days after the stroke. For these subjects, study duration will be through 30±7 days post stroke.
Subject Inclusion Criteria	All eligible subjects should be approached for participation in the trial. Subjects who meet all of the following criteria will be evaluated for enrollment in this trial, provided no exclusion criterion (below) is met. IC1. Subject has documented aortic valve stenosis and is treated with an approved TAVR device via transfemoral access. IC2. Subject has the recommended artery diameter at the site of filter placement per the Sentinel® Cerebral Protection System Instructions For Use: 9–15 mm for the brachiocephalic artery and 6.5–10 mm in the left common carotid artery. IC3. Subject (or legal representative) provides written informed consent.
Subject Exclusion Criteria	Subjects who meet any one of the following criteria (listed as contraindications in the Sentinel® Cerebral Protection System IFU) will be excluded from this clinical trial. EC1. Subject has arterial stenosis >70% in either the left common carotid artery or the brachiocephalic artery. EC2. Subject's brachiocephalic or left carotid artery reveals significant stenosis, ectasia, dissection, or aneurysm at the aortic ostium or within 3 cm of the aortic ostium. EC3. Subject has compromised blood flow to the right upper extremity. EC4. Subject has access vessels with excessive tortuosity. EC5. Subject has uncorrected bleeding disorders.

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	EC6. Subject is contraindicated for anticoagulant and antiplatelet therapy. ***Note 4*:** Use of general anesthesia during TAVR may affect neurocognitive function shortly after the procedure. While not an exclusion criterion, it is recommended that general anesthesia not be used if possible.
Adjunctive Pharmacologic Therapy	Management of subjects in both groups, including antiplatelet and anticoagulant medications, is left to the discretion of the treating physician.
Statistical Methods	
Analysis Sets	Analysis sets are listed below. Intention-To-Treat (ITT): This population includes all subjects who sign an ICF and are enrolled in the trial (randomized), whether or not the assigned treatment is received. Per-Protocol: This population includes all ITT subjects who undergo TAVR and who are treated as assigned in the randomization process (excludes crossovers).
Statistical Hypothesis for the Primary Endpoint	The rate of the primary endpoint (all stroke through 72 hours post TAVR procedure or hospital discharge [whichever comes first] as adjudicated by an independent CEC) in the Sentinel (Test) cohort is superior to that in the Control cohort.
Statistical Test Method for the Primary Endpoint	A chi-square test will be used to test the two-sided hypothesis of superiority of Sentinel versus the Control: H_0: $P_{Sentinel} = P_{Control}$ H_1: $P_{Sentinel} \neq P_{Control}$ where $P_{Sentinel}$ and $P_{Control}$ correspond to the rates of the primary endpoint for the Sentinel group (test) and the Control group (no cerebral protection), respectively. The primary analysis set is the ITT analysis set; this endpoint will also be analyzed for the Per-Protocol analysis set.
Sample Size Parameters for the Primary Endpoint	Sample size parameters are listed below. • Expected Control rate $P_{Control}$: 4% • Expected Sentinel (test) rate $P_{Sentinel}$: 2% (50% relative reduction)

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	• Test significance level (α): 0.05 (2-sided) • Power ($1-\beta$): > 0.90 (see ***Note 5*** below) • Test to Control ratio: 1:1 (see ***Note 6*** below) • Number of evaluable subjects: Maximum enrollment of up to 6000 with sample size re-estimation[d] • Planned enrollment: 3000 (N=1500 per cohort) The statistical approach uses an adaptive group sequential design. There will be 1 planned formal interim analysis performed on the first 70% of enrolled subjects (N=2100) by the Independent Safety and Statistical Monitor. The study will be stopped if a significant difference in favor of the test arm is observed after this interim analysis. Based on the results of the interim analysis, sample size re-estimation[d] may be performed and the sample size may be increased up to a maximum of 6000 subjects. Details of this adaptive approach are pre-specified in the Independent Safety and Statistical Monitor charter. A final analysis will be performed on all enrolled subjects if the study is not stopped after the interim analysis. ***Note 5*:** Power calculation includes sample size re-estimation[d] ***Note 6*:** To avoid selection/treatment bias, randomization will occur at the index procedure (prior to procedural puncture/incision). d: Mehta CR and Pocock SJ. Statist Med 2011;30:3267–3284 Mehta CR, et al. Circulation 2009;119:597–605
Success Criteria for the Primary Endpoint	One planned formal interim analysis for the primary endpoint will be conducted on the first 70% of enrolled subjects (N=2100). A final analysis will be conducted on all enrolled subjects if the study is not stopped after the interim analysis. The Lan-Demets spending function[e] with O'Brien-Fleming boundaries is used to adjust the alpha-level for the interim analysis and the final analysis: 0.0148 and 0.0455, respectively. If the *P* value from the chi square test is less than alpha and the rate in the Sentinel group is less than the rate in the Control group, the Sentinel group will be concluded to have a lower rate of all stroke through 72 hours or discharge (whichever comes first) versus the Control group. e: Kim K and DeMets DL. Biometrika 1987;74:149–154 EAST® 6.5 Software, Cytel, Inc. 2018

3. Table of Contents

3.1. *Table of Figures*

3.2. *Table of Tables*

4. Introduction

This protocol specifies procedures and contains information relevant to the postmarket multicenter PROTECTED TAVR randomized controlled trial (PROTECTED TAVR: Stroke PROTECTion with SEntinel During Transcatheter Aortic Valve Replacement). The study device is the Sentinel® Cerebral Protection System (Sentinel) designed and manufactured by Boston Scientific Corporation, Marlborough, MA, USA (BSC). It is a percutaneously delivered filter device designed to capture any debris or thrombus that may embolize to the innominate and left common carotid arteries during a transcatheter aortic valve replacement (TAVR) procedure. The objective of the study is to demonstrate that use of Sentinel significantly reduces the risk of post-TAVR peri-procedural (≤72 hours) stroke.

4.1. *Background*

Stroke is a feared occurrence that can complicate both surgical and catheter-based therapies for aortic stenosis[1,2]. With first generation TAVR devices, the reported incidence of major stroke within 30 days ranged from 3% to 7%[3]. Increased short-term and long-term mortality have been associated with post-TAVR stroke[4,5]. Growing operator experience and improved device designs have lowered but not eliminated the TAVR stroke risk[6].

Cerebral embolic protection devices (CEPD) are intended to prevent cerebral embolization and have demonstrated efficacy in carotid and saphenous vein graft stenting with clinically significant reductions in mortality, stroke, and myocardial infarction[7-9]. Use of CEPD is an emerging strategy to mitigate post-TAVR neurologic risk[10] and 5 randomized controlled trials (RCT) have directly investigated the safety and efficacy of CEPD in TAVR (protection devices include the Sentinel® Cerebral Protection System [Sentinel], Claret Montage™ Dual Filter System [an earlier iteration of Sentinel], TriGuard™ HDH Embolic Deflection Device, and EMBOL-X™ Intra-aortic Filter)[11-15]. Four of these RCTs assessed 100 or fewer subjects. In the multicenter DEFLECT III RCT (TriGuard; N=85), the primary safety endpoint (death, stroke, life-threatening or disabling bleeding, stage 2 or 3 acute kidney injury, or major vascular complications) was numerically lower in the protected cohort (21.7% versus 30.8%, P=0.34)[14]. Subjects with complete three-vessel cerebral coverage had fewer new neurologic deficits detected by the National Institutes of Health Stroke Scale (NIHSS; 3.1% vs. 15.4%) and a >2-fold increase in recovery of normal cognitive function (Montreal Cognitive Assessment [MoCA] score >26) at 30 days. In a single-center RCT (N=30), use of EMBOL-X appeared to reduce both the incidence and volume of new cerebral lesions[15]. In another single-center RCT (CLEAN-TAVI; N=100), use of Claret Montage was associated with a significant reduction ($P < 0.001$) in the number of new lesions[13]. In the multicenter MISTRAL-C RCT (N=65), use of Sentinel resulted in fewer new lesions and a smaller total lesion volume as well as less neurocognitive deterioration (4% vs. 27%, P=0.017)[12].

The pivotal multicenter SENTINEL RCT was larger (N=363) than the aforementioned RCTs and showed that Sentinel use during TAVR was safe with no increased procedural complications[11]. Subjects were prospectively randomized 1:1:1 into a safety arm (N=123, Sentinel only) and 2 imaging cohorts (device arm [N=121] and control arm without Sentinel [N=119]). The primary safety endpoint was 30-day major adverse cardiac and

cerebrovascular events (MACCE; defined as all death, all stroke, and stage 3 acute kidney injury [AKI] per Valve Academic Research Consortium [VARC-2] definitions[16]). Stroke occurrence was assessed by NIHSS and modified Rankin scale (mRS) score as administered by a neurologist. In the combined safety and device arms, the MACCE rate of 7.3% was non-inferior ($P < 0.001$) to the prespecified performance goal of 18.3% and similar to the control rate (9.9%; $P=0.41$). As Sentinel is a temporary accessory device, a post hoc analysis was performed to assess stroke at the time most applicable to device usage. The stroke rate at ≤72 hours was 3.0% in the combined safety and device arms compared to 8.2% in the control arm, demonstrating a relative reduction of 63% in stroke rates in favor of Sentinel. At 30 days, event rates for subjects with Sentinel were similar to rates in the control arm for mortality (1.3% vs. 1.8%, respectively, $P=0.25$), stroke (5.6% vs. 9.1%, $P=0.25$), stage 3 AKI (0.4% vs. 0.0%, $P=1.00$), and major vascular complications (8.6% vs. 5.9%, $P=0.53$).

The primary efficacy endpoint in the SENTINEL RCT was reduction in median total new lesion volume in protected territories in the device versus the control arm. This was assessed by diffusion-weighted magnetic resonance imaging (MRI) at 2 to 7 days after TAVR. This quantitative MRI analysis was intended to serve as a surrogate endpoint for the clinically meaningful endpoint of stroke. While the median total new lesion volume in protected territories was 42% lower in subjects with Sentinel, the new MRI lesion volume (102.8 mm^3) was not significantly different from that of the control group (178.0 mm^3, $P=0.33$). Notably, randomization was not stratified by valve category and MRI results in the control arm as well as the response to embolic protection appeared to differ with varying TAVR systems. Post-hoc multivariable analyses of MRI data also indicated that the T2/fluid-attenuated inversion recovery (FLAIR) lesion volume at baseline, a marker of previous injury and gliosis, was the strongest predictor of new lesion volume after TAVR. After adjusting for valve type, baseline T2/FLAIR lesion volume, and an interaction between valve type and treatment arm, there were significant reductions in new lesion volume in the device versus control arms (protected territories: $P=0.025$, all territories: $P=0.050$)[11]. Debris was found within the study device filters in 99% of subjects in the SENTINEL RCT. The debris components included acute thrombus with tissue elements, artery wall, valve tissue, calcification, and foreign materials.

Published reports have also described use of CEPD with TAVR in real-world experiences. In the single-center SENTINEL-Ulm registry, the Sentinel device was used in 280 of 802 (34.9%) consecutive patients. In a propensity-matched population (N=280 with Sentinel, N=280 unprotected), use of Sentinel was associated with a 70% reduction in the odds of death or stroke within 7 days of TAVR (odds ratio [OR] 0.30, 95% confidence interval [CI] 0.12–0.77; 2.1% vs. 6.8%, $P=0.01$)[17]. The overall stroke rate was reduced from 4.6% to 1.4% with Sentinel ($P=0.03$, OR 0.29, 95% CI 0.10–0.93) and there was a significant reduction in disabling stroke (3.2% vs. 0.4%, $P=0.01$). Stroke within 48 hours of TAVR was also significantly lower with Sentinel (1.1%) compared with unprotected procedures (3.6%, $P=0.03$). By multivariate analysis, TAVR without protection was an independent risk factor for stroke within 7 days ($P=0.04$)[17]. In a 2-center registry in the Netherlands (333 propensity-matched pairs), patients with Sentinel experienced fewer neurological events (stroke and transient ischemia attack [TIA]) compared to those without protection at 24 hours post TAVR (0.9% vs. 3.6%; $P=0.035$) and at 30 days (2.7% vs. 6.6%; $P=0.029$)[18]. There were

significantly fewer disabling strokes in protected patients at 30 days (0.9% vs. 4.2%; *P*=0.039). By multiple regression analysis, use of Sentinel was associated with fewer neurological events at 24 hours after TAVR (*P*=0.015, OR 0.20, 95% CI 0.06–0.73). Patients who experienced a clinically significant neurological event underwent computed tomographic (CT) analysis of the brain. At 24 hours post TAVR, patients in the Sentinel cohort had fewer neurological events (2 of 3 [67%]) in the protected areas of the brain (those not dependent on the left vertebral artery) compared to patients without Sentinel (10 of 12 [83%]). After 24 hours the localization of new neurological events was similar between the 2 cohorts[18].

The randomized trials mentioned above were not powered to demonstrate a reduction in stroke rates. A recent study-level meta-analysis with these RCTs found that use of CEPD was associated with a nonsignificant trend towards lower risk for death or stroke on both relative (6.1% vs. 9.6%; relative risk: 0.61; 95% confidence interval [CI]: 0.35 to 1.07; *P*=0.08; I^2=0%) and absolute (absolute risk difference: –3.5%; 95% CI: –7.9% to 0.9%; number needed to treat: 28) terms[19]. Outcomes were recently reported from a patient level pooled analysis of subjects from the SENTINEL and CLEAN-TAVI RCTs, and the SENTINEL-Ulm registry[20]. Propensity score matching was performed to adjust for possible confounders (N=553 per cohort). In patients undergoing TAVR with Sentinel, the stroke rate within 72 hours was significantly reduced compared with unprotected procedures (1.88% vs. 5.44%, OR 0.35, 95% CI 0.17–0.72, relative risk reduction 65%, absolute risk reduction 3.54%; *P*=0.0028). The authors noted that their findings suggest that TAVR with Sentinel is associated with a significantly lower rate of periprocedural stroke compared to unprotected TAVR. They remarked, however, that due to differences in methodology between the studies, results should be considered hypothesis generating and to prove the hypothesis, a large RCT on use of CEPD in TAVR is required.

Based on observations in the SENTINEL trial, the United States Food and Drug Administration (FDA) in June 2017 approved the Sentinel® Cerebral Protection System for use in TAVR as a cerebral protection device to capture and remove embolic material while performing transcatheter aortic valve procedures in order to reduce ischemic injury to the brain peri-procedurally. However, while results from the SENTINEL trial provided reassuring evidence of the safety of dual-filter neuroprotection therapy and confirmed the high frequency of embolic debris capture, the effectiveness of the Sentinel CEPD at reducing stroke risk after TAVR remains uncertain.

4.2. *Study Rationale*

As noted above, although Sentinel was approved by FDA for capturing debris during TAVR, the pivotal RCT missed its primary endpoint. In the same trial, post hoc analysis showed clinical benefit with reduction in procedural stroke. However, prospective data to prove clinical benefit are lacking. The objective of the PROTECTED TAVR study is to demonstrate that use of Sentinel significantly reduces the risk of peri-procedural stroke (≤72 hours) after TAVR.

5. Commercial Device Description (part of Standard of Care)

The Sentinel® Cerebral Protection System is indicated for use as a cerebral protection device to capture and remove embolic material while performing transcatheter aortic valve procedures in order to reduce ischemic injury to the brain peri-procedurally.

5.1. *Overview of the Sentinel® Cerebral Protection System*

The commercially available Sentinel Cerebral Protection System (Sentinel; Boston Scientific Corporation, Marlborough, MA, USA) is designed to capture and remove debris dislodged during endovascular procedures. It consists of 2 filters within a single 6-F delivery catheter percutaneously placed from the right radial or brachial artery over a 0.014-inch guidewire.

The major features of the system are shown in **Figure 5.1-1**. The articulating sheath tip, proximal sheath tip, proximal filter hoop, proximal articulating sheath marker, distal filter hoop and distal filter tip are radiopaque to enable visualization during use. The filters are positioned in the brachiocephalic artery (proximal filter) and the left common carotid artery (distal filter) before the TAVR procedure (**Figure 5.1-2**) and are withdrawn into the catheter and removed after TAVR. Additional product information can be found in the commercial Instructions For Use (IFU).

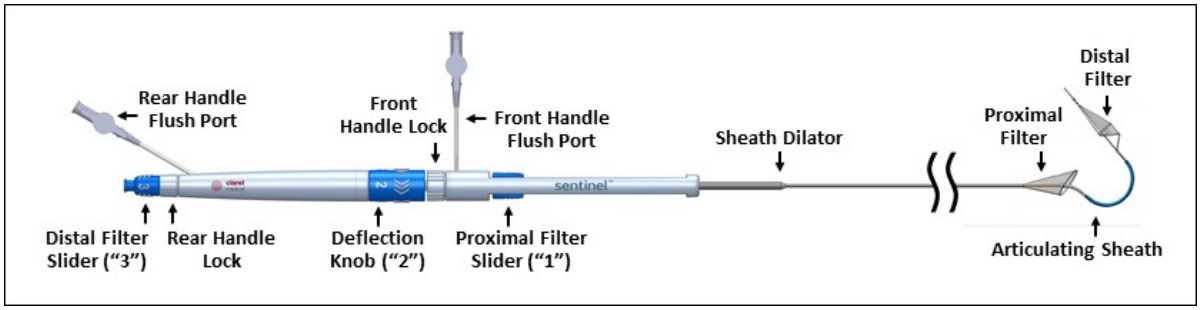


Figure 5.1-1: Diagram of the Sentinel System

The pore size of the filters is 140 µm.

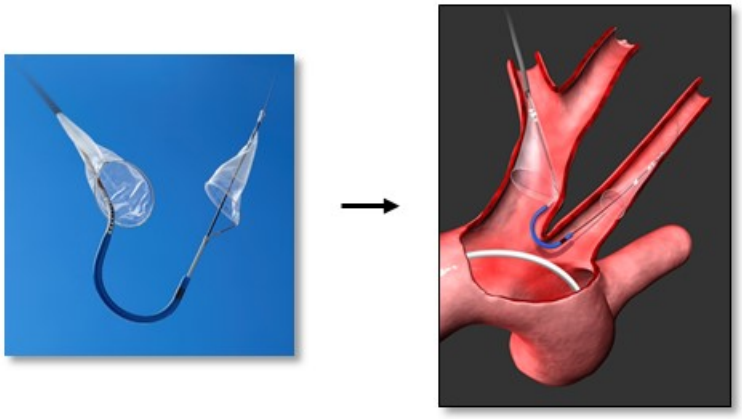


Figure 5.1-2: Positioning of the Sentinel Device

The proximal filter is placed in the brachiocephalic artery and the distal filter is placed in the left carotid artery.

5.2. *Device Labeling*

A basic description of the device and a comprehensive set of instructions (IFU) are contained in each product package.

6. Study Objectives and Endpoints

6.1. *Study Objectives*

The objective of the PROTECTED TAVR study is to demonstrate that use of the Sentinel® Cerebral Protection System significantly reduces the risk of peri-procedural stroke (≤72 hours) after transcatheter aortic valve replacement (TAVR).

6.2. *Study Endpoints*

Outcomes will be assessed on an intention-to-treat (ITT) basis and on a per-protocol basis. The ITT analysis set includes all subjects who sign an Informed Consent Form (ICF; see Section **20**) approved by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC)/Human Research Ethics Committee (HREC) and are enrolled upon randomization (see Section **9.1** for point of enrollment), whether or not the assigned treatment is received. The Per-Protocol analysis set includes all ITT subjects who receive the assigned treatment (excludes crossovers).

6.2.1. Primary Endpoint

The primary endpoint is all stroke (hemorrhagic, ischemic, or undetermined status) through 72 hours post TAVR procedure or discharge (whichever comes first) as adjudicated by an independent Clinical Events Committee (CEC) and using Neurologic Academic Research Consortium (NeuroARC)[21] definitions.

The primary analysis set for the primary endpoint is the ITT analysis set.

6.2.2. Additional Measurements

The additional measurements shown below are based on NeuroARC[21] and Valve Academic Research Consortium (VARC)[16,22] endpoints and definitions and will be assessed through 72 hours post TAVR procedure or discharge (whichever comes first). Mortality (cardiovascular and non-cardiovascular), neurological endpoints (stroke, transient ischemic attack [TIA], and delirium), acute kidney injury, and Sentinel access site major vascular complications will be adjudicated by an independent CEC.

- All-cause death (cardiovascular and non-cardiovascular)
- Neurological endpoints (see **Note 1** below)
  - Stroke (disabling and non-disabling)
  - Transient ischemic attack

- Delirium

- Safety composite of all-cause mortality and all stroke
- Neurological status as determined by the following (see **Note 1** below):
  - Neurological physical examination
  - Modified Rankin Scale (mRS) score
  - National Institutes of Health Stroke Scale (NIHSS)
  - Confusion Assessment Method for Intensive Care Unit Patients (CAM-ICU)[23,24]
  - Montreal Cognitive Assessment (MoCA)[25]
- Acute kidney injury based on the AKIN System[26] Stage 3 (including renal replacement therapy) and Stage 2
- Sentinel access site vascular complications related to the procedure (major and minor)
- Sentinel system acute delivery and retrieval (categorized as successful deployment of both filters, 1 filter, or no filter and retrieval of the system)
- Health status as evaluated by EQ-5D[27,28] Quality of Life questionnaire at baseline

Note 1: The neurological physical examination must be carried out by a neurology professional (board certified/board eligible neurologist, neurology fellow, neurology physician assistant, or neurology nurse practitioner). The NIHSS, mRS, and MoCA must be performed by certified personnel. The CAM-ICU must be done by personnel with appropriate training as documented by the sponsor. In all subjects where stroke is suspected, a formal neurology/stroke consult should be obtained, and the subject should be further assessed and treated per standard of care. In subjects diagnosed with post-procedural stroke, mRS must also be administered 30±7 days following the stroke; the simplified mRS questionnaire[29] may be used for this follow-up assessment.

6.3. *Overview of Objectives and Endpoints*

Table 6.3-1 provides an overview of the aforementioned study objectives and endpoints and a rationale for the specific endpoints.

Table 6.3-1: Overview of Objectives and Endpoints

Objective	Endpoint	Rationale for Endpoint
Primary Endpoint		
Evaluate effectiveness of the cerebral protection device during TAVR procedures	All stroke to 72 hours post-TAVR procedure	Demonstrate significant reduction of peri-procedural stroke (≤72 hours) after TAVR, which is a critical acute safety event observed in the population undergoing TAVR.
Additional Measurements of Safety and Effectiveness		
Evaluate safety of the cerebral protection device	Safety measures peri- and post- TAVR procedure and at discharge	Confirm safety based on assessments recommended by VARC[16,22] and NeuroARC[21] for this elderly population.

Table 6.3-1: Overview of Objectives and Endpoints

Objective	Endpoint	Rationale for Endpoint
Evaluate effectiveness of the cerebral protection device	Device performance and other effectiveness measures peri- and post TAVR procedure and at discharge	Effectiveness assessments recommended by VARC[16,22] and NeuroARC[21] for this elderly population.

Abbreviation: NeuroARC=Neurologic Academic Research Consortium; TAVR=transcatheter aortic valve replacement; VARC=Valve Academic Research Consortium

7. Study Design

PROTECTED TAVR is a prospective, post-market, multicenter randomized controlled trial (RCT) evaluating use of the Sentinel® Cerebral Protection System in subjects with aortic valve stenosis who are treated with an approved TAVR device.

7.1. *Scale and Duration*

An initial enrollment of up to 3000 randomized subjects in up to 100 study centers is planned (see **Note 1** below). A single center may enroll up to 15% of the total enrollment; approval from the Sponsor is required for additional enrollment. Subjects to be treated via a transfemoral approach with a commercially available TAVR device will be randomized 1:1 into a Test cohort using the commercially available Sentinel or a Control cohort with no cerebral protection system. A subject who provides an ICF signed by the subject or the subject's legally authorized representative is considered enrolled in the study upon randomization, which will occur at the index procedure prior to procedural puncture/incision. The study duration for each subject is expected to be through 72 hours or hospital discharge, whichever comes first. In subjects diagnosed with a stroke, mRS must be administered at 30±7 days after the stroke. For these subjects, study duration will be through 30±7 days post stroke.

Note 1: If sample size re-estimation is needed (see Section **11.1.1.2**), the planned maximum enrollment will be up to 6000 randomized subjects.

Figure 7.1-1 summarizes the study design. The treating physician must be a trained, experienced Sentinel user. Every subject must be deemed treatable with the Sentinel device (have suitable anatomy per the Sentinel Instructions For Use [IFU]). All eligible subjects (see Section **8**) should be approached for participation in the trial.

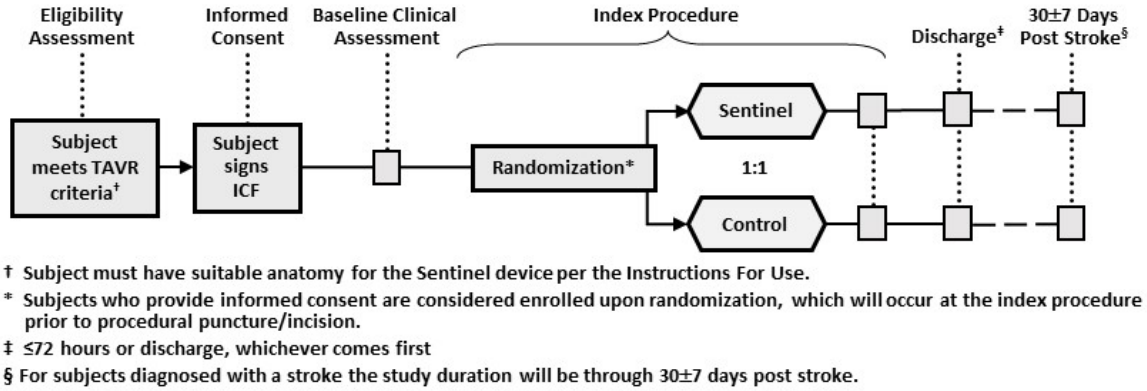


Figure 7.1-1: PROTECTED TAVR Study Design Summary

The planned initial enrollment of 3000 subjects is expected to be completed in approximately 30 months; therefore, the study duration is estimated to be less than 32 months (see **Note 1** in Section **6.2.2** regarding subjects diagnosed with a stroke). Enrollment may be extended based on the planned interim analysis (see Section **11.1.1.2**).

The PROTECTED TAVR study will be registered at ClinicalTrials.gov prior to enrollment of the first subject.

7.2. *Treatment Assignment*

Subjects who are to be treated with a commercially available TAVR device and who have suitable anatomy for the Sentinel device will be randomized 1:1 into a Test cohort using the commercially available Sentinel or a Control cohort with no cerebral protection system. Randomization will occur at the index procedure (prior to procedural puncture/incision) to avoid selection/treatment bias. The randomization schedules will be computer-generated, using a pseudo-random number generator. Randomization will be stratified by center, by operative risk, and by intended TAVR valve type (Section **11.2.4**). All randomized subjects will have unique identification numbers. Random permuted blocks will be employed to ensure approximate balance of treatment allocation within each stratum. Instructions on randomization are provided in the Manual of Operations. See Section **5** for a detailed description of the Sentinel device.

7.3. *Justification for the Study Design*

In order to support the stated objectives of this study (see Section **6.1**) while also limiting the potential exposure of study subjects to risk, an initial enrollment of up to 3000 randomized subjects at up to 100 centers in North America, Europe, and Australia is planned. Treating physicians will be appropriately trained and have relevant clinical experience with the Sentinel device before enrolling trial subjects. Safety and effectiveness results will be reported on all enrolled subjects (see Section **19** for information on safety reporting). One planned formal interim analysis for the primary endpoint will be conducted on the first 70%

of enrolled subjects (N=2100). The study will be stopped early if a significant difference in favor of the test arm is observed after this interim analysis.

Management of subjects in both groups, including antiplatelet and anticoagulant medications, will be left to the discretion of the treating physician in this post-market study.

8. Subject Selection

Subjects will be evaluated for eligibility for commercial TAVR by the center heart team per the local standard of practice. All eligible subjects should be approached for participation in PROTECTED TAVR. Subjects who meet all of the inclusion criteria (see Section **8.1**) will be evaluated for enrollment in this trial, provided no exclusion criterion (see Section **8.2**) is met. All subjects will have unique identification numbers.

8.1. *Inclusion Criteria*

Subjects who meet all of the following criteria (**Table 8.1-1**) may be given consideration for inclusion in this clinical investigation, provided no exclusion criterion (see **Table 8.2-1**) is met.

Table 8.1-1: PROTECTED TAVR Inclusion Criteria

IC1. Subject has documented aortic valve stenosis and is treated with an approved transcatheter aortic valve replacement device via transfemoral access.
IC2. Subject has the recommended artery diameter at the site of filter placement per the Sentinel® Cerebral Protection System Instructions For Use: 9–15 mm for the brachiocephalic artery and 6.5–10 mm in the left common carotid artery as determined by computed tomography or per local standard of care.
IC3. Subject (or legal representative) provides written informed consent.

8.2. *Exclusion Criteria*

Subjects who meet any one of the criteria in **Table 8.2-1** (listed as contraindications in the Sentinel® Cerebral Protection System IFU) will be excluded from this clinical study.

Table 8.2-1: PROTECTED TAVR Exclusion Criteria

EC1. Subject has arterial stenosis >70% in either the left common carotid artery or the brachiocephalic artery.
EC2. Subject's brachiocephalic or left carotid artery reveals significant stenosis, ectasia, dissection, or aneurysm at the aortic ostium or within 3 cm of the aortic ostium.
EC3. Subject has compromised blood flow to the right upper extremity.
EC4. Subject has access vessels with excessive tortuosity.
EC5. Subject has uncorrected bleeding disorders.
EC6. Subject is contraindicated for anticoagulant and antiplatelet therapy.
Note: Use of general anesthesia during TAVR may affect neurocognitive function shortly after the

Table 8.2-1: PROTECTED TAVR Exclusion Criteria

procedure. While not an exclusion criterion, it is recommended that general anesthesia not be used if possible.

9. Subject Accountability

9.1. *Point of Enrollment*

A subject who provides an ICF signed by the subject or the subject's legally authorized representative is considered enrolled in the study upon randomization, which will occur at the index procedure prior to procedural puncture/incision.

9.2. *Withdrawal*

All subjects enrolled in the clinical study (including those withdrawn from the clinical study) shall be accounted for and documented. If a subject withdraws from the clinical investigation the reason(s) shall be reported. Reasons for withdrawal include but are not limited to physician discretion, subject choice to withdraw consent, or death. If such withdrawal is due to problems related to device safety or performance, the investigator shall ask for the subject's permission to follow his/her status/condition outside of the clinical study.

While all efforts will be made to minimize attrition, subjects may withdraw from the study at any time, with or without reason, and without prejudice to further treatment. Withdrawn subjects will not undergo any additional study follow-up, nor will they be replaced. The investigator may discontinue a subject from participation in the study if the investigator feels that the subject can no longer fully comply with the requirements of the study or if any of the study procedures are deemed potentially harmful to the subject. Data that have already been collected on withdrawn subjects will be retained and may be used for analysis, unless local regulations apply. No new data will be collected after subject withdrawal.

All applicable case report forms up to the point of subject withdrawal and an "End of Study" form for the subject must be completed. If the withdrawal is due to investigator discretion, the investigator should follow-up with the subject per standard of care.

9.3. *End-of-Study Definition*

This clinical study will be considered completed when the last subject has concluded assessments as outlined in the data collection schedule in **Table 10.1-1** (see **Note 1** below).

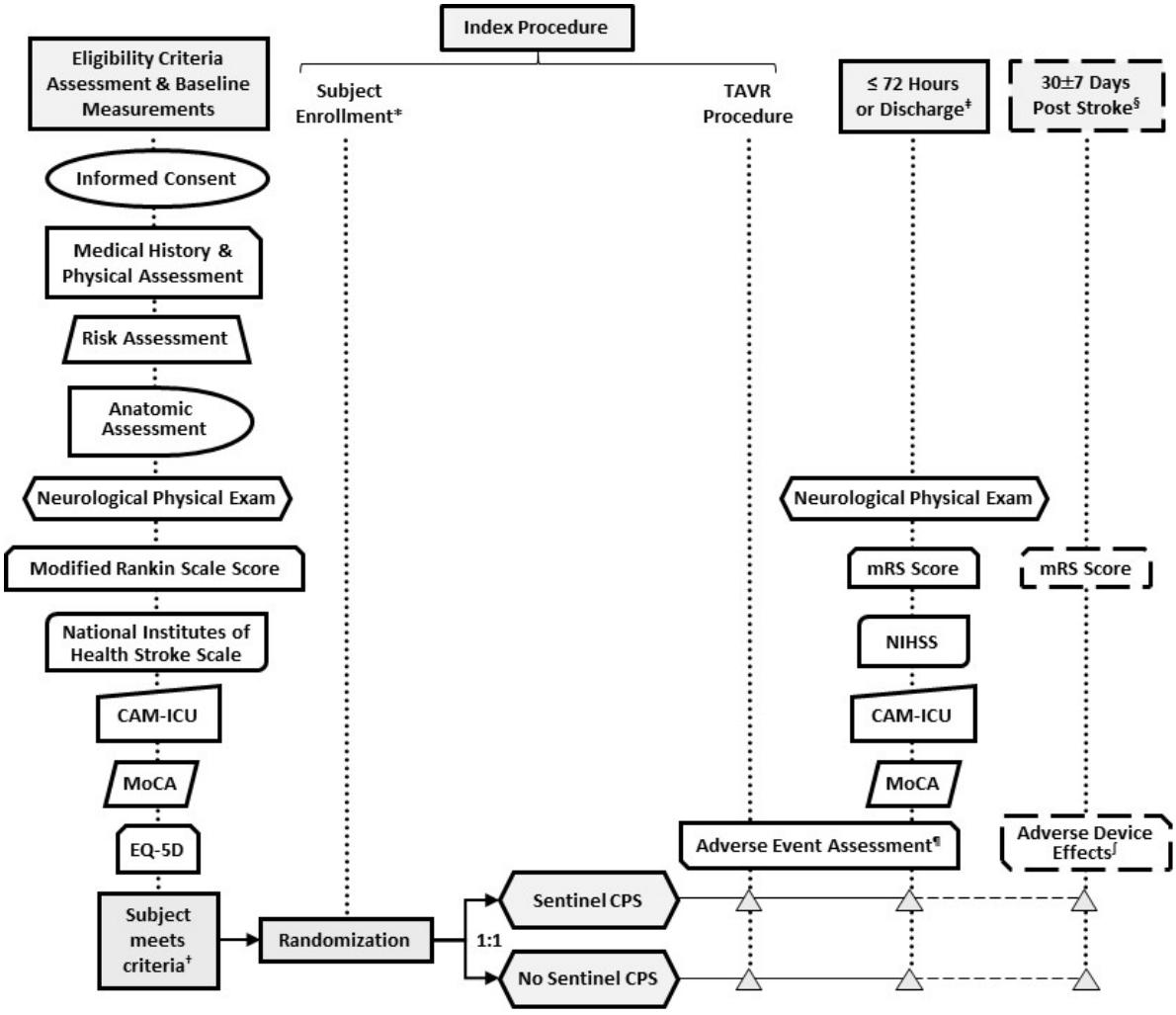
Note 1: In subjects diagnosed with a stroke, mRS must be administered at 30±7 days after the stroke; mortality plus device related adverse events (including adverse device effects [ADE], serious adverse device effects [SADE], unanticipated adverse device effects [UADE], and unanticipated serious adverse device effects [USADE]; see Section **19**) through 30±7 days post stroke must be reported to BSC. For these subjects, study duration will be through 30±7 days post stroke.

10. Study Methods

10.1. *Data Collection*

This section indicates the data needed to fulfill the objectives of this clinical study. Boston Scientific Corporation considers data collected from clinical trial subjects to be personal data (see definitions of different data categories in **Table 25.2-1**) and compliance with privacy and data protection laws and regulations (for example, the General Data Protection Regulation [GDPR], see **Table 25.2-1**) to be critically important. Data collection for this clinical study has been carefully considered to comply with data privacy laws.

The data collection schedule is shown in **Figure 10.1-1** and in **Table 10.1-1**. Additional information is provided in Section **10.2** through Section **10.9**. The methods are based on NeuroARC metrics[21], VARC metrics[16,22], and/or guideline recommendations[30-32].



† Subject must have suitable anatomy for the Sentinel device per the Instructions For Use.

* Subjects who provide informed consent are considered enrolled upon randomization, which will occur at the index procedure prior to procedural puncture/incision.

‡ ≤72 hours or discharge, whichever comes first

§ For subjects diagnosed with a stroke the study duration will be through 30±7 days post stroke.

¶ Includes SAE, ADE, SADE, UADE, USADE, device deficiencies, and CEC events

∫ Includes mortality, ADE, SADE, UADE and USADE

Figure 10.1-1: PROTECTED TAVR Study Event Schedule

See **Table 10.1-1** for additional information.

Abbreviations: ADE=adverse device effect; CAM-ICU=Confusion Assessment Method for Intensive Care Unit Patients; CEC=Clinical Events Committee; CPS=cerebral protection system; CT=computed tomography; MoCA=Montreal Cognitive Assessment; NIHSS=National Institutes of Health Stroke Scale; SADE=serious adverse device effect; SAE=serious adverse event; UADE=unanticipated adverse device effect; USADE=unanticipated serious adverse device effect; TAVR=transcatheter aortic valve replacement

Table 10.1-1: PROTECTED TAVR Study Event Schedule

Assessment	Baseline[a]	Index Procedure	≤72 Hours / Discharge	30±7 Days Post Stroke[b]
Signed Informed Consent Form	X	–	–	–
Clinical Assessments				
Demographics and medical history	X	–	–	–
Physical assessment	X	–	–	–
Risk assessment[c]	X	–	–	–
Imaging Assessments				
Anatomic suitability for the Sentinel device[d]	X	–	–	–
Neurological Assessments[e]				
Neurological physical examination[f]	X	–	X	–
Modified Rankin Scale score[g]	X	–	X	X[b]
NIHSS[g]	X	–	X	–
CAM-ICU[h]	X	–	X	–
MoCA[i]	X	–	X	–
Quality of Life Survey[j]	X			
Adverse event assessment	–	X[k]	X[k]	X[b]

Note 1: X = should be performed, – = not required.

a: Within 30 days prior to index procedure (unless otherwise specified).

b: In all subjects where stroke is suspected, a formal neurology/stroke consult should be obtained, and the subject should be further assessed and treated per standard of care. In subjects diagnosed with post-procedural stroke, mRS must also be administered at 30±7 days after the stroke; the simplified mRS questionnaire[29] may be used for this follow-up evaluation. In these subjects, mortality and an assessment of device related adverse events (ADE, SADE, UADE, and USADE; see **Table 25.2-1** for definitions) must be reported to BSC from the time of enrollment through 30±7 days post stroke.

c: Data from the STS[33] risk score assessment must be collected (see definition of surgical risk in **Table 25.2-1**); euroSCORE II[34] risk score data may be collected if performed per local standard of care; height and weight must be collected (to determine body mass index).

d: Anatomic assessment must be carried out using CT or per local standard of care to determine if subject has the recommended artery diameter at the site of filter placement per the study Inclusion Criteria (**Table 8.1-1**).

e: Follow-up neurological assessments must be performed within 72 hours post index procedure but may be performed earlier if deemed necessary. These post-procedure assessments should be performed only when the subject is no longer drowsy from procedural medication.

f: Assessment must be carried out by a neurology professional (board certified/board eligible neurologist, neurology fellow, neurology physician assistant, or neurology nurse practitioner).

g: Assessment must be carried out by certified personnel.

h: The Confusion Assessment Method for ICU Patients (CAM-ICU)[23,24] should be done at baseline and on day 1 post procedure; it must be performed by personnel with appropriate training as documented by the sponsor.

i: The Montreal Cognitive Assessment[25] (MoCA) must be carried out by certified personnel.

j: EQ-5D questionnaire is conducted at baseline[27,28]

k: The adverse event assessment includes SAE, ADE, SADE, UADE, USADE, device deficiencies, and CEC events; safety events will be monitored and reported to BSC from the time of enrollment through 72 hours or subject discharge (whichever comes first). Please refer to Section **19.1** for reportable events,

Table 10.1-1: PROTECTED TAVR Study Event Schedule

Assessment	Baseline[a]	Index Procedure	≤72 Hours / Discharge	30±7 Days Post Stroke[b]

including a list of CEC events, and to **Table 25.2-1** for definitions of these events, which specify data required for CEC adjudication.

Abbreviations: ADE=adverse device effect; BSC=Boston Scientific Corporation; CAM-ICU=Confusion Assessment Method for Intensive Care Unit Patients; CEC=Clinical Events Committee; CT=computed tomography; MoCA=Montreal Cognitive Assessment; mRS=modified Rankin Scale; NIHSS=National Institutes of Health Stroke Scale; SADE=serious adverse device effect; SAE=serious adverse event; STS=Society of Thoracic Surgeons; UADE=unanticipated adverse device effect; USADE=unanticipated serious adverse device effect

10.2. *Study Subject Screening*

Subjects will be evaluated for eligibility for commercial TAVR by the center heart team per the local standard of practice. Subjects with documented aortic valve stenosis who are to be treated with a commercially available TAVR device and who sign the IRB/IEC/HREC-approved ICF will be assessed for enrollment in the clinical study. Inclusion and exclusion criteria are provided in Section **8**. Every subject must be deemed treatable with the Sentinel study device.

Once written informed consent has been obtained, a subject will be entered into a screening log, which will be maintained at the center. A subject who provides written informed consent will be entered into the screening log whether or not the subject is randomized into the study. For consented subjects not enrolled in the trial, the reason for screen failure will be documented in the screening log.

It is estimated that nearly 5% of elderly ≥75 years of age have aortic stenosis and its prevalence is expected to increase due to an aging population[35,36]. Because aortic stenosis most commonly occurs in the very elderly, women are well represented in TAVR studies. As the very elderly will represent the majority of enrolled subjects, traditionally underrepresented populations are expected to be included in the subject population as allowed by governing law/national regulation.

10.3. *Subject Informed Consent*

Written informed consent (see Section **20**) must be obtained for all qualified subjects who are potential study candidates prior to the subject's index procedure.

The Investigator/designee who has been trained on the protocol will explain the nature and scope of the study, potential risks and benefits of participation, and answer questions for the subject. If the subject agrees to participate, the IRB/IEC/HREC-approved ICF must be signed and personally dated by the subject or his/her legally authorized representative. The Investigator/designee must also sign the ICF prior to subject enrollment. Any additional persons required by the center's IRB/IEC/HREC to sign the ICF must also comply.

10.4. *Baseline Assessments*

The following assessments must be completed within 30 days prior to the index procedure per local standard of care for TAVR unless otherwise indicated. The study electronic case report forms (eCRFs) identify the specific data points to be collected.

- Confirmation of eligibility and contraindications per the Sentinel® Cerebral Protection System IFU (see **Note 1** below)
- Clinical assessments
  - Demographics including age and gender
  - Medical history
  - Physical assessment
  - Risk assessments
    - Society of Thoracic Surgeons (STS) risk score[33]
    - EuroSCORE II[34] (if performed per local standard of care)
    - Nutritional assessment (height and weight)
- Imaging assessments
  - Anatomic suitability for the Sentinel device (computed tomography [CT] assessment as performed per local standard of care)
- Neurological assessments
  - Neurological physical exam (see **Note 2** below)
  - mRS score (see **Note 2** below)
  - NIHSS score (see **Note 2** below)
  - CAM-ICU (see **Note 3** below)
  - MoCA (see **Note 4** below)
- Quality of Life Survey (EQ-5D[27,28]) should be administered within 30 days prior to the procedure

Note 1: Every subject must be deemed treatable with the Sentinel device (have suitable anatomy per the IFU).

Note 2: The neurological physical exam must be performed by a neurology professional (board certified/board eligible neurologist, neurology physician assistant, or neurology nurse practitioner). The NIHSS and mRS must be performed by certified personnel (external certification for NIHSS; internal or external certification for mRS).

Note 3: The delirium assessment consists of the Confusion Assessment Method for ICU Patients (CAM-ICU)[23,24] and must be performed by personnel with appropriate training as documented by the sponsor.

Note 4: The cognitive assessment consists of the Montreal Cognitive Assessment[25](MoCA) and must be carried out by certified personnel (external certification).

10.5. *Index Procedure*

The preparation of the subject for the percutaneous procedure will be performed following standard techniques. Refer to the Sentinel IFU for instructions on preparation and use of the cerebral protection system test device. Refer to the specific valve Directions/Instructions For Use for instructions on preparation and placement of the commercial TAVR valve. Subject randomization will occur prior to procedural puncture/incision; see Section **11.2.4** for information on stratification. Study device deficiencies and safety events during the procedure (includes SAE, SADE, UADE, USADE, ADE, and CEC events; see Section **19**) along with the associated treatment must be reported to BSC. The end of the index procedure is defined as vessel closure and hemostatic control.

Note 1: Use of general anesthesia during TAVR may affect neurocognitive function shortly after the procedure. While not an exclusion criterion, it is recommended that general anesthesia not be used if possible.

10.6. *Post-Procedure (≤ 72 Hours)/Prior to Hospital Discharge*

Within 72 hours post TAVR procedure or before discharge (whichever comes first), the following neurological assessments must be performed (see **Note 1** below).

- Neurological physical exam (see **Note 2** in Section **10.4** and **Note 2** below)
- mRS score (see **Note 2** in Section **10.4** and **Note 2** below)
- NIHSS score (see **Note 2** in Section **10.4** and **Note 2** below)
- CAM-ICU (see **Note 3** in Section **10.4** and **Note 3** below)
- MoCA (see **Note 4** in Section **10.4**)

Note 1: Follow-up neurological assessments must be performed within 72 hours post TAVR procedure but may be performed earlier if deemed necessary. These post-procedure assessments should be performed only when the subject is no longer drowsy from procedural medication. The neurological assessor should be blinded to the subject's cerebral protection device treatment group.

Note 2: In all subjects where stroke is suspected, a formal neurology/stroke consult should be obtained, and the subject should be further assessed and treated per standard of care. In subjects diagnosed with post-procedural stroke, mRS must also be administered at 30±7 days following the stroke (see Section **10.7** below). The simplified mRS questionnaire[29] may be used for this follow-up assessment.

Note 3: This delirium assessment should be done on day 1 post TAVR procedure.

A complete safety event assessment, including any SAE, ADE, SADE, UADE, USADE, device deficiency with associated treatment, and any CEC event regardless of seriousness and device relationship (see Section **19**) must be carried out and reported to BSC from the time of enrollment through 72 hours post TAVR procedure or subject discharge (whichever

comes first). Please see Section **10.7** below for additional information regarding subjects with stroke.

The subject may be discharged from the hospital when clinically stable, at the Investigator's discretion per local standard of care. Pharmacologic management of subjects in both treatment groups, including antiplatelet and anticoagulant medications, is left to the discretion of the treating physician.

10.7. *Post-Stroke (30±7 Days)*

In all subjects where stroke is suspected (≤72 hours post TAVR procedure or through discharge, whichever comes first), a formal neurology/stroke consult should be obtained, and the subject should be further assessed and treated per standard of care. In subjects diagnosed with post-procedural stroke, mRS must also be administered at 30±7 days after the stroke. The simplified mRS questionnaire[29] may be used for this follow-up assessment. For subjects with stroke, mortality plus device related adverse events (ADE, SADE, UADE, and USADE; see **Table 25.2-1** for definitions) through 30±7 days post stroke must be reported to BSC.

10.8. *Study Completion*

All subjects will be followed through 72 hours post TAVR procedure or hospital discharge (whichever comes first). A subject's participation in the study will be considered complete after 72 hours or hospital discharge (whichever comes first). See Section **10.7** regarding additional follow-up for subjects who experience a stroke. For those subjects, study duration will be through 30±7 days after the stroke.

10.9. *Source Documents*

It is preferable that original source documents, when available, are maintained at the investigative center. In lieu of original source documents, certified copies are required to be maintained. A certified copy is a copy (irrespective of the type of media used) of the original record that has been verified (i.e., by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original. Source documentation includes but is not limited to those items noted in **Table 10.9-1**. Source documentation provided to the Sponsor for assessment/adjudication will be deidentified per local law and regulations.

Table 10.9-1: Source Documentation Requirements

Requirement	Disposition
Printed, optical, or electronic document containing source data. Examples may include but are not limited to: hospital records, laboratory notes, device accountability records, photographic negatives, radiographs, records kept at the investigation center, at the laboratories and at the medico-technical departments involved in the clinical investigation.	Retain at center.

Note: Please see **Table 25.2-1** for definitions of "source data" and "source document."

11. Statistical Considerations

11.1. *Endpoints*

11.1.1. Primary Endpoint

The study is powered to assess the primary endpoint, which is all stroke (hemorrhagic, ischemic, or undetermined status; disabling or nondisabling) through 72 hours post TAVR procedure or hospital discharge (whichever comes first) as adjudicated by an independent CEC using NeuroARC definitions.

11.1.1.1. Statistical Hypothesis for the Primary Endpoint

The primary statistical hypothesis is that the rate of the primary endpoint (all stroke through 72 hours post TAVR procedure or discharge [whichever comes first]) in the Sentinel (Test) cohort is superior to that in the Control cohort. The null and alternative hypotheses for the primary endpoint are as follows:

H_0: $P_{Sentinel} = P_{Control}$

H_1: $P_{Sentinel} \neq P_{Control}$

where $P_{Sentinel}$ and $P_{Control}$ correspond to the rates of the primary endpoint for the Sentinel cohort (test) and the Control cohort (no cerebral protection), respectively.

Testing will be done for the primary endpoint as described in the statistical analysis plan. A chi-square test will be used. The primary analysis population for the primary endpoint is the ITT analysis set; this endpoint will also be analyzed for the Per-Protocol analysis set (see Section **11.2.1** for description of analysis sets).

11.1.1.2. Sample Size Parameters for the Primary Endpoint

The sample size parameters for the primary endpoint are shown below.

- Expected Control rate $P_{Control}$: 4%
- Expected Sentinel (test) rate $P_{Sentinel}$: 2% (50% relative reduction)
- Test significance level (α): 0.05 (2-sided)
- Power ($1 - \beta$): > 0.90 (see **Note 1** below)
- Test to Control ratio: 1:1 (see **Note 2** below)
- Number of evaluable subjects: up to 6000 maximum enrollment with sample size re-estimation[37,38]
- Planned enrollment: = 3000 subjects (N=1500 per cohort)

The statistical approach uses an adaptive group sequential design[37,38]. There will be 1 planned formal interim analysis performed on the first 70% of enrolled subjects (N=2100) by the Independent Safety and Statistical Monitor (see Section **21.3**). The study will be stopped if a significant difference in favor of the test arm is observed after this interim analysis.

Based on the results of the interim analysis, sample size re-estimation[37,38] may be performed and the sample size may be increased up to a maximum of 6000 subjects. Details of this adaptive approach are pre-specified in the Independent Safety and Statistical Monitor charter. A final analysis will be performed on all enrolled subjects if the study is not stopped after the interim analysis (see Section **11.1.1.3** and Section **11.3.2** below).

Note 1: This power calculation includes sample size re-estimation[37,38].

Note 2: Randomization will occur at the index procedure (prior to procedural puncture/incision) to avoid selection/treatment bias.

11.1.1.3. Success Criteria for the Primary Endpoint

As noted above, 1 planned formal interim analysis for the primary endpoint will be conducted on the first 70% of enrolled subjects and a final analysis will be conducted on all enrolled subjects if the study is not stopped after the interim analysis. The alpha-level for the interim analysis and the final analysis is adjusted using the Lan-Demets spending function with O'Brien-Fleming boundaries[39,40] as detailed below in Section **11.3.2**. If the *P* value from the chi square test is less than alpha and the rate in the Sentinel group is less than the rate in the Control group, the group with Sentinel will be concluded to have a lower rate of all stroke through 72 hours post TAVR procedure or hospital discharge (whichever comes first) compared to the Control group.

11.1.1.4. Statistical Methods – Primary Endpoint

All subjects who are enrolled will be eligible for evaluation. Handling of dropouts and missing data will depend on their frequency and the nature of the outcome measure. Methods to eliminate or minimize bias will be implemented and described completely, if applicable. Outlier values will be evaluated for their validity. Suspected invalid data will be queried and corrected in the database prior to statistical analysis.

11.1.2. Post-procedure Measurements

Post-procedure data will be collected as detailed in the clinical study schedule (**Table 10.1-1**) and will be summarized using descriptive statistics for continuous variables (e.g., mean, standard deviation, n, minimum, maximum) and frequency tables or proportions for discrete variables. Adverse event and SAE rates will be reported.

11.2. *General Statistical Methods*

All statistical analyses will be performed using the SAS System software, version 9.2 or later (Copyright© 2000 SAS Institute Inc., SAS Campus Drive, Cary, North Carolina 27513, USA. All rights reserved).

All statistical analyses will be conducted according to applicable Standard Operating Procedures, Work Instructions, and the study-specific statistical analysis plan.

11.2.1. Analysis Sets

The primary endpoint and the additional measurements will be analyzed on an ITT basis and a Per-Protocol basis. For ITT analyses, all subjects who sign the IRB/IEC/HREC-approved study ICF (see Section **10.3**) and are enrolled in the trial (see Section **9.1**) will be included in the analysis, whether or not the assigned treatment is received. For Per-Protocol analyses, ITT subjects who undergo TAVR and who are treated as assigned in the randomization process (excludes crossovers) will be included in the analysis.

11.2.2. Control of Systematic Error/Bias

The selection of subjects will be made from the Investigator's usual case load. All subjects who have signed the ICF, are deemed treatable with the Sentinel device (have suitable anatomy per the IFU) and are selected to undergo TAVR with a commercial TAVR device will be eligible for enrollment in the study. The study center's heart team assessments and imaging measurements before device placement will contribute to the determination of subject eligibility for the study.

To control for inter-observer variability, an independent CEC (see Section **21.1**) will adjudicate pre-determined endpoints.

11.2.3. Number of Subjects per Investigative Center

A single center may enroll up to 15% of the total enrollment; approval from the Sponsor is required for additional enrollment.

11.2.4. Randomization Scheme

Using a computer-generated list of random treatment allocations (i.e., a randomization schedule) subjects to be treated with a commercially available TAVR device will be randomized 1:1 into a Test cohort using the commercially available Sentinel device or a Control cohort with no cerebral protection system. Randomization will be stratified by center, by operative risk (low risk and intermediate or higher risk; see surgical risk definitions in **Table 25.2-1**), and by intended TAVR valve type (balloon-expandable device and non-balloon expandable device). Additional information is provided in the study Manual of Operations.

11.3. *Data Analyses*

Baseline and outcome variables will be summarized using descriptive statistics for continuous variables (mean, standard deviation, number of observations, minimum and maximum) and discrete variables (percentage and count/sample). See Section **11.1.1** for a discussion on analysis of the primary endpoint.

11.3.1. Other Endpoints/Measurements

Other measurements not driven by statistical hypotheses are listed in Section **6.2.2**.

11.3.2. Interim Analyses

One formal interim analysis is planned for the purpose of stopping this trial early for effectiveness. This analysis will be performed by the Independent Safety and Statistical Monitor (see Section **21.3**). The interim analysis for the primary endpoint will be conducted on the first 70% of enrolled subjects; a final analysis will be conducted on all enrolled subjects if the study is not stopped after the interim analysis.

The Lan-Demets spending function with O'Brien-Fleming boundaries[39] is used to adjust the alpha-level for the interim analysis and the final analysis (if needed): 0.0148 and 0.0455, respectively. If the *P* value from the chi-square test is less than alpha, and the rate in the Sentinel group is less than the rate in the Control group, the group with Sentinel will be concluded to have a lower rate of all stroke through 72 hours post TAVR procedure or discharge (whichever comes first) versus the Control group and the study will be stopped. If the study is not stopped after the interim analysis, sample size re-estimation may be performed contingent on the results of the interim analysis (see Section **11.1.1.2**).

The planned interim analysis is pre-specified to provide a formal hypothesis testing approach to examine the primary endpoint with the adjusted significance level and stop the trial early for effectiveness if appropriate. This pre-specified interim analysis allows for sample size re-estimation per the study's adaptive group sequential design[37,38].

Additional analyses not defined in the protocol may also be conducted for regulatory agency review.

11.3.3. Subgroup Analyses

The primary endpoint and pre-specified additional measurements (see Section **6.2**) will be summarized for the following subgroups.

- Operative risk (low, intermediate, high/extreme; treatment by subgroup interaction analysis)
- Gender

No adjustments for multiple comparisons will be made. Additional subgroup analyses may be performed as appropriate.

11.3.4. Justification of Pooling

Analyses for the primary endpoint will be presented using data pooled across centers and intended TAVR valve types. An assessment of the poolability of subjects across centers and intended TAVR valve types will be made using logistic regression. Main effects for the center (intended TAVR valve type) and treatment and the interaction of the center (intended TAVR valve type) by treatment will be included in separate logistic regression models with the primary endpoint as the outcome. If the *P* value for center (intended TAVR valve type) by treatment interaction is ≥0.1, it can be concluded that the treatment effect is not different across the centers (intended TAVR valve types) and the data can be pooled. In the analysis to justify pooling across centers, the centers with fewer than 10 subjects enrolled in the study

will be combined into "virtual centers" based on geographic region so that "virtual centers" have ≥10 subjects but no more than the largest enrolling center.

11.3.5. Changes to Planned Analyses

Any changes to the planned statistical analyses made prior to performing the analyses will be documented in an amended statistical analysis plan approved before performing the analyses. Changes from the planned statistical methods after performing the analyses will be documented in the clinical study report along with a reason for the change.

12. Health Economics Outcomes

A formal health economics analysis may be completed as part of this study, provided meaningful healthcare resource utilization data are obtained. This will take into consideration healthcare resource utilization through discharge (with a maximum of 30 days if the subject is hospitalized for longer than 30 days) for both the Test and Control groups. Medical billing information (e.g., UB-04 billing claim form) through the TAVR index hospitalization may be collected at centers in the United States for health economics analyses.

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. Only personnel trained and authorized will have access to the system.

The clinical database will reside on a production server hosted by Medidata EDC System (New York, NY, USA). All changes made to the clinical data will be captured in an electronic audit trail and available for review by 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 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 BSC 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 Medidata EDC system and will be issued to the center for appropriate response. Center staff will be responsible for resolving all queries in the database.

13.2. *Data Retention*

The Principal Investigator or his/her designee or investigational center will maintain all essential study documents and source documentation that support the data collected on the study subjects in compliance with applicable regulatory requirements.

The Principal Investigator or his/her designee will take measures to prevent accidental or premature destruction of these documents. If for any reason the Principal Investigator or his/her designee 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. Centers are required to inform BSC in writing where paper or electronic files are maintained in case files are stored off site and are not readily available.

14. Deviations

An Investigator must not make any changes or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency. An investigator shall notify BSC and the reviewing IRB/IEC/HREC of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency, and those deviations which affect the scientific integrity of the clinical investigation. Such notice shall be given as soon as possible, but no later than 5 working days after the emergency occurred, or per prevailing local requirements, if sooner than 5 working days.

All deviations from the investigational plan, with the reason for the deviation and the date of occurrence, must be documented and reported to BSC using the EDC eCRF. Centers may also be required to report deviations to the IRB/IEC/HREC, per local guidelines and government regulations.

Deviations will be reviewed and evaluated on an ongoing basis and, as necessary, appropriate corrective and preventive actions (including IRB/IEC/HREC notification, center re-training, or center discontinuation/termination) will be put into place by BSC.

15. Device Accountability

The Sentinel® Cerebral Protection System is a commercially available product. The study eCRF identifies the required device information.

16. Compliance

16.1. *Statement of Compliance*

The PROTECTED TAVR study will be conducted in accordance with 21 CFR Parts 11, 50, and 54; the relevant parts of the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practices (GCP); the International Standard ISO 14155 Clinical

Investigation of Medical Devices for Human Subjects – Good Clinical Practice; ethical principles that have their origins in the Declaration of Helsinki; and pertinent individual country/state/local laws and regulations. The study shall not begin until the required approval/favorable opinion from the IRB/IEC/HREC and/or regulatory authority has been obtained, if appropriate. Investigator responsibilities are detailed in Section **16.2**.

16.2. *Investigator Responsibilities*

The Principal Investigator of an investigational center is responsible for ensuring that the study is conducted in accordance with the Clinical Study Agreement, the clinical investigation plan/protocol, ISO 14155 or ICH/GCP, ethical principles that have their origins in the Declaration of Helsinki, any conditions of approval imposed by the reviewing IRB/IEC/HREC, and prevailing local and/or country laws and/or regulations, whichever affords the greater protection to the subject.

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

- Prior to beginning the study, sign the Clinical Study Agreement and comply with the Investigator responsibilities as described in such Agreement.
- Provide his/her qualifications and experience to assume responsibility for the proper conduct of the study and that of key members of the site team through up-to-date curriculum vitae or other relevant documentation and disclose potential conflicts of interest, including financial, that may interfere with the conduct of the clinical study or interpretation of results.
- Complete commercial training requirements associated with the Sentinel® Cerebral Protection System.
- Make no changes in or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency; document and explain any deviation from the approved protocol that occurred during the course of the clinical investigation.
- Create and maintain source documents throughout the clinical study and ensure their availability with direct access during monitoring visits or audits; ensure that all clinical-investigation-related records are retained per requirements.
- Ensure the accuracy, completeness, legibility, and timeliness of the data reported to BSC in the CRFs and in all required reports.
- Record, report, and assess (seriousness and relationship to the device/procedure) every adverse event as applicable per the protocol and observed device deficiency.
- Report to BSC, per the protocol requirements, all ADEs, SAEs, SADEs, USADEs, CEC events, and device deficiencies.
- Report to the IRB/IEC/HREC and regulatory authorities any SAEs and device deficiencies that could have led to a SADE and potential USADE, if required by applicable laws or regulations or this protocol or by the IRB/IEC/HREC, and supply

BSC with any additional requested information related to the safety reporting of a particular event.

- Allow BSC and its representatives to perform monitoring and auditing activities and be accessible to the clinical research monitor or auditor and respond to questions during monitoring visits or audit(s).
- Allow and support regulatory authorities and the IRB/IEC/HREC when performing auditing activities.
- Ensure that informed consent is obtained in accordance with applicable laws, this protocol, and local IRB/IEC/HREC requirements.
- Provide adequate medical care to a subject during and after a subject's participation in a clinical study in the case of adverse events, as described in the ICF.
- Inform the subject of the nature and possible cause of any adverse events experienced.
- Inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required.
- Provide the subject with well-defined procedures for possible emergency situations related to the clinical study, and make the necessary arrangements for emergency treatment, including decoding procedures for blinded/masked clinical investigations, as needed.
- Ensure that clinical medical records are clearly marked to indicate that the subject is enrolled in this clinical study.
- Ensure that, if appropriate, subjects enrolled in the clinical investigation are provided with some means of showing their participation in the clinical investigation, together with identification and compliance information for concomitant treatment measures (contact address and telephone numbers shall be provided).
- Inform, with the subject's approval or when required by national regulations, the subject's personal physician about the subject's participation in the clinical investigation.
- Make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from clinical investigation while fully respecting the subject's rights.
- Ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation.

16.2.1. Delegation of Responsibility

When specific tasks are delegated by an investigator, including but not limited to conducting the informed consent process, the Principal Investigator is responsible for providing appropriate training, so the delegate is competent to perform the tasks they have been delegated and adequate supervision of those to whom tasks are delegated. Where there is a sub-investigator at a center, the sub-investigator should not be delegated the primary

supervisory responsibility for the center. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

16.3. *Institutional Review Board/Independent Ethics Committee*

The investigational center will obtain the written and dated approval/favorable opinion of the IRB/IEC/HREC for the clinical investigation before recruiting subjects and implementing all subsequent amendments, if required.

A copy of the written IRB/IEC/HREC and/or competent authority approval of the protocol (or permission to conduct the study) and ICF must be received by BSC before recruitment of subjects into the study. Prior approval must also be obtained for other materials related to subject recruitment or which will be provided to the subject.

Any amendment to the protocol will require review and approval by the IRB/IEC/HREC before the changes are implemented in the study. All changes to the ICF will be IRB/IEC/HREC approved; a determination will be made regarding whether a new ICF needs to be obtained from subjects who provided consent using a previously approved ICF.

Annual IRB/IEC/HREC approval and renewals will be obtained throughout the duration of the study as required by applicable local/country laws or regulations or IRB/IEC/HREC requirements. Copies of the study reports and the IRB/IEC/HREC continuance of approval must be provided to BSC.

16.4. *Sponsor Responsibilities*

All information and data sent to BSC concerning subjects or their participation in this study will be considered confidential by BSC and will be kept confidential in accordance with all applicable laws and regulations. Only authorized BSC personnel and/or a BSC representative including, but not limited to, a contract research organization [CRO]) will have access to this information. 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, such as overseeing and improving the performance of its device, new medical research, and proposals for developing new medical products and procedures. All data used in the analysis and reporting of this study or shared with a third-party researcher will be without identifiable reference to specific subjects.

Information received during the study will not be used to market to subjects; subject names will not be placed on any mailing lists or sold to anyone for marketing purposes.

16.4.1. Role of Boston Scientific Corporation Representatives

Boston Scientific Corporation personnel (including field clinical engineers) who are trained in the use of the Sentinel Cerebral Protection System will provide training and technical support to the investigator and other healthcare professionals (collectively HCP) as needed (see Section **16.4.2**), 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 observing testing or medical procedures to provide information relevant to the IFU.

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 investigator.
- 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

16.4.2. Training

Boston Scientific has established a commercial training program to provide the physicians and staff with the information and experience necessary to control user-associated risks when the Sentinel Cerebral Protection System is used in accordance with the commercial IFU. In the current study, treating physicians will have already received the required training and have relevant clinical experience with the Sentinel device before enrolling trial subjects. Personnel involved in the administration of the neurocognitive examinations (MoCA), the delirium assessments (CAM-ICU), and the NIHSS and mRS stroke assessments will undergo the necessary study training and, where applicable, confirmation will be provided to show that the personnel are appropriately certified to administer such exams.

16.5. *Insurance*

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

17. Monitoring

Monitoring will be performed during the study to assess continued compliance with the protocol and applicable regulations. In addition, the clinical research monitor verifies that study records are adequately maintained, that data are reported in a satisfactory manner with respect to timeliness, adequacy, and accuracy, and that the Principal Investigator continues to have sufficient staff and facilities to conduct the study safely and effectively. The Principal Investigator/institution guarantees direct access to original source documents by BSC personnel, their designees, and appropriate regulatory authorities.

The study may also be subject to a quality assurance audit by BSC or its designees, as well as inspection by appropriate regulatory authorities. It is important that the Principal Investigator

and relevant study personnel are available during on-site monitoring visits or audits and that sufficient time is devoted to the process.

18. Potential Risks and Benefits

18.1. *Instructions for Use*

Please refer to the Sentinel Cerebral Protection System IFU for an overview of anticipated adverse (device) effects, and risks associated with the commercial device.

18.2. *Risks Associated with Participation in the Clinical Study*

Risks associated with TAVR and use of the commercial Sentinel Cerebral Protection System are listed in the IFU and in the ICF. There are no incremental risks associated with participation in this clinical study.

18.3. *Possible Interactions with Concomitant Medical Treatments*

Medications to be used in PROTECTED TAVR constitute standard of care for TAVR as described in society guidelines[30,31].

18.4. *Risk Minimization Actions*

Additional risks may exist. Risks can be minimized through compliance with this protocol, performing procedures in the appropriate hospital environment, adherence to subject selection criteria, close monitoring of the subject's physiologic status during research procedures and/or follow-ups and by promptly supplying BSC with all pertinent information required by this protocol.

Data will be monitored as they are submitted to BSC. Qualified employees of BSC, or a designee under contract, will conduct monitoring visits at the initiation of the study and at interim intervals described in the monitoring plan throughout the course of the study to evaluate protocol compliance and determine if there are any issues that could affect the safety or welfare of any subject in the study. A dynamic safety review process including CEC (Section **21.1)** adjudication of specified events as recommended by VARC[16,22] and/or NeuroARC[21] will support risk mitigation.

18.5. *Anticipated Benefits*

It is expected that the commercially available Sentinel Cerebral Protection System may provide benefit to the subject by capturing potentially harmful embolic debris liberated during the TAVR procedure. Without such protection, embolic debris could travel unimpeded via the cerebral circulation to the brain; this could lead to cerebral vascular events such as stroke and/or TIA.

19. Safety Reporting

19.1. *Reportable Events by Investigational Center to Boston Scientific*

It is the responsibility of the investigator to assess and report to BSC any event that occurs in any of following categories:

- All serious adverse events (SAE)
- All device-related adverse events
- All device deficiencies
- Unanticipated adverse device effects (UADE)/unanticipated serious adverse device effects (USADE)
- All CEC events (see below)
- New findings/updates in relation to already reported events

When possible, the medical diagnosis should be reported as the Event Term instead of individual symptoms.

If it is unclear whether or not an event fits one of the above categories, or if the event cannot be isolated from the device or procedure, it should be submitted as an adverse event (AE) and/or device deficiency.

Any AE required by the protocol, experienced by the study subject after informed consent and once considered enrolled in the study, whether during or subsequent to the procedure, must be recorded in the eCRF. Collection of safety events includes all CEC events (see below), regardless of seriousness and device relationship.

Underlying diseases are not reported as AEs unless there is an increase in severity or frequency during the course of the investigation. Death should not be recorded as an AE but should only be reflected as an outcome of one (1) specific SAE (see **Table 19.2-1** for AE definitions).

Refer to the Instructions For Use for the known risks associated with the commercial device.

The endpoints (see endpoint definitions in **Table 25.2-1**) requiring adjudication by the CEC include the following.

- Death: cardiovascular and non-cardiovascular
- Stroke: disabling and non-disabling
- Transient ischemic attack
- Delirium
- Acute kidney injury (Stage 2 and Stage 3)
- Sentinel access site major vascular complications related to the procedure

Details on the CEC events and procedures are outlined in the CEC charter. Tests and images required to adjudicate these events are specified in the event definitions (see **Table 25.2-1**).

19.2. *Definitions and Classification*

Adverse event definitions are provided in **Table 19.2-1**. Administrative edits were made to the safety definitions from ISO 14155 and MEDDEV 2.7/3 for clarification purposes.

Table 19.2-1: Safety Definitions

Term	Definition
Adverse Event (AE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, whether or not related to the study medical device. **Note 1:** This includes events related to the study medical device or comparator. **Note 2:** This definition includes events related to the procedures involved. **Note 3:** For users or other persons, this definition is restricted to events related to the study medical device.
Adverse Device Effect (ADE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Adverse event related to the use of the study medical device **Note 1:** This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the study medical device. **Note 2:** This definition includes any event resulting from use error or intentional abnormal use of the study medical device.
Serious Adverse Event (SAE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	**Note 1:** This definition meets the reporting objectives and requirements of ISO 14155 and MEDDEV 2.7/3. Adverse event that: a) Led to death, b) Led to serious deterioration in the health of the subject as defined by either: 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, or 3) in-patient hospitalization or prolongation of existing hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function c) Led to fetal distress, fetal death, or a congenital abnormality or birth defect. **Note 2:** Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without a serious deterioration in health, is not considered a serious adverse event.
Serious Adverse Device Effect (SADE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated Adverse Device Effect (UADE) *Ref: 21 CFR Part 812*	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

Table 19.2-1: Safety Definitions

Term	Definition
	application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.
Unanticipated Serious Adverse Device Effect (USADE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report. **Note**: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.
Device Deficiency *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	An inadequacy of the study medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer.

19.3. *Relationship to Device(s)*

The Investigator must assess the relationship of the reportable AE to the Sentinel System or procedure. See criteria in **Table 19.3-1**.

Table 19.3-1: Criteria for Assessing Relationship of Study Device or Procedure to Adverse Event

Classification	Description
Not Related *Ref: MEDDEV 2.7/3*	Relationship to the device or procedures can be excluded when: • the event is not a known side effect of the product category the device belongs to or of similar devices and procedures; • the event has no temporal relationship with the use of the study device or the procedures; • the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; • the discontinuation of medical device application or the reduction of the level of activation/exposure – when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event; • the event involves a body-site or an organ not expected to be affected by the device or procedure; • the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/clinical condition, an effect of another device, drug, treatment or other risk factors); • the event does not depend on a false result given by the study device used for diagnosis, when applicable; harms to the subject are not clearly due to use error; • In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

Table 19.3-1: Criteria for Assessing Relationship of Study Device or Procedure to Adverse Event

Classification	Description
Unlikely Related *Ref: MEDDEV 2.7/3*	The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
Possibly Related *Ref: MEDDEV 2.7/3*	The relationship with the use of the study device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.
Probably Related *Ref: MEDDEV 2.7/3*	The relationship with the use of the study device seems relevant and/or the event cannot be reasonably explained by another cause, but additional information may be obtained.
Causal Relationship *Ref: MEDDEV 2.7/3*	The serious event is associated with the study device or with procedures beyond reasonable doubt when: • the event is a known side effect of the product category the device belongs to or of similar devices and procedures; • the event has a temporal relationship with the study device use/application or procedures; • the event involves a body-site or organ that - the study device or procedures are applied to; - the study device or procedures have an effect on; • the serious event follows a known response pattern to the medical device (if the response pattern is previously known); • the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible); • other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; • harm to the subject is due to error in use; • the event depends on a false result given by the study device used for diagnosis, when applicable; • In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

19.4. *Investigator Reporting Requirements*

The communication requirements for reporting to BSC are as shown in **Table 19.4-1**.

Table 19.4-1: Investigator Reporting Requirements

Event Classification	**Communication Method**	**Communication Timeline (post-market studies)** (MEDDEV 2.12/2: GUIDELINES ON A MEDICAL DEVICE VIGILANCE SYSTEM)
Unanticipated Adverse Device Effect (UADE) Unanticipated Serious Adverse Device Effect (USADE)	Complete AE eCRF page with all available new and updated information.	• Within 1 business day of first becoming aware of the event. • Terminating at the end of the study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• At request of Sponsor.
Serious Adverse Event (SAE) Clinical Events Committee Event (see Section **19.1**) (CEC event)	Complete AE eCRF page with all available new and updated information.	• Within 10 business days after becoming aware of the event or as per local/regional regulations. • Reporting required through the end of the study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• When documentation is available
Serious Adverse Device Effect (SADE) and serious VARC event	Complete AE eCRF page with all available new and updated information.	• Within 2 business days of first becoming aware of the event or as per local/regional regulations. • Reporting required through the end of the study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• When documentation is available
Device Deficiencies (including but not limited to failures, malfunctions, and product nonconformities) **Note:** Any device deficiency that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable event.	Complete applicable CRF fields/forms with all available new and updated information.	• Within 1 business day of first becoming aware of the event. • Reporting required through the end of the study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• At request of Sponsor

Table 19.4-1: Investigator Reporting Requirements

Event Classification	Communication Method	Communication Timeline (post-market studies) (MEDDEV 2.12/2: GUIDELINES ON A MEDICAL DEVICE VIGILANCE SYSTEM)
Adverse Event (AE) including Adverse Device Effect (ADE) and non-serious VARC event	Complete AE eCRF page, which contains such information as date of AE, treatment of AE, resolution, assessment of seriousness and relationship to the device.	• In a timely manner (e.g., recommend within 10 business days) after becoming aware of the information • Reporting required through the end of the study
	Provide all relevant source documentation (de-identified/pseudonymized) for reported event.	• At request of Sponsor

Abbreviations: AE=adverse event; eCRF=electronic case report form; VARC=Valve Academic Research Consortium

19.5. *Boston Scientific Device Deficiencies*

Device deficiencies (Sentinel) will be documented and reported to BSC. If possible, the device(s) should be returned to BSC for analysis. Instructions for returning the device(s) will be provided in the investigative site files. Device deficiencies should also be documented in the subject's source records.

Device deficiencies are not adverse events. However, an AE that results from a device deficiency would be recorded as an AE on the appropriate eCRF.

19.6. *Reporting to Regulatory Authorities / IRBs and IECs / Investigators*

Boston Scientific Corporation is responsible for reporting adverse event information to all participating Principal Investigators, IRBs/IECs, and regulatory authorities, as applicable according to local reporting requirements.

The Principal Investigator is responsible for informing the IRB/IEC/HREC and regulatory authorities of UADEs/USADEs and SAEs as required by local/regional regulations.

20. Informed Consent

Subject participation in this clinical study is voluntary. Informed Consent is required from each subject or his/her legally authorized representative. The Investigator is responsible for ensuring that Informed Consent is obtained prior to the use of any study 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 IRB/IEC/HREC and/or Regulatory authority, as applicable. The ICF must be accepted by BSC or its delegate (e.g., CRO), and approved by the center's IRB/IEC/HREC or central IRB/IEC/HREC, if applicable.

Boston Scientific Corporation 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/IEC/HREC. Any modification requires acceptance 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/IEC/HREC 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 at a minimum include the following steps, as well as any other steps required by applicable laws, rules, regulations and guidelines:

- 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 competent to sign the ICF under the applicable laws, rules, regulations and guidelines and by the investigator and/or an authorized designee responsible for conducting the informed consent process. If a legal representative signs the ICF, 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 authority according to their requirements. Any violations of the informed consent process must be reported as deviations to the sponsor and local regulatory authorities (e.g., IRB/IEC/HREC), 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 applicable laws, protocol, a change in Principal Investigator, administrative changes, or following annual review by the IRB/IEC/HREC. The new version of the ICF must be approved by the IRB/IEC/HREC. Acceptance by Boston Scientific is required if changes to the revised ICF are requested by the center's IRB/IEC/HREC. The IRB/IEC/HREC will determine the subject population to be re-consented.

21. Committees

21.1. *Safety Monitoring Process*

To promote early detection of safety issues, the Clinical Events Committee (CEC; see below) 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 BSC or its designee, which is responsible for coordinating the collection of information for the subject dossier from the centers and core laboratory. During regularly scheduled monitoring visits clinical research monitors will support the dynamic reporting process through their review of source documents and other data information. The BSC Medical Safety group includes physicians with expertise in cardiology and with the necessary therapeutic and subject matter expertise to evaluate and classify the events into the categories outlined above (Section **19**).

21.1.1. Clinical Events Committee

A CEC will be used in this study. The CEC is an independent group of individuals with pertinent expertise, including cardiovascular interventional therapy, cardiovascular surgery, and neurology, which 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 and adjudicate study endpoint related clinical events. The responsibilities, qualifications, membership, and committee procedures of the CEC are outlined in the CEC Charter.

21.2. *Steering Committee*

A Steering Committee consisting of Sponsor Clinical Management, the Study Coordinating PIs, a neurologist, cardiac surgeons, and other investigators experienced in TAVR will be convened. Responsibilities may include oversight of the overall conduct of the study with regard to protocol development, study progress, subject safety, overall data quality and integrity, as well as disseminating any study results through appropriate scientific sessions and publications. Steering Committee members may participate in the review and approval of all requests for data analysis, abstract and manuscript preparation and submission.

21.3. *Independent Safety and Statistical Monitor*

The unblinded data from the first 70% of enrolled subjects will be reviewed by the Independent Safety and Statistical Monitor (independent of the project team). The study will be stopped if a significant difference in favor of the test arm is observed after this interim analysis (see Section **11.3.2**). Based on the results of the interim analysis, sample size re-estimation[37,38] may be performed and the sample size may be increased up to a maximum of 6000 subjects. Details of this adaptive approach are pre-specified in the Independent Safety and Statistical Monitor charter.

22. Suspension or Termination

22.1. *Premature Termination of the Study*

Boston Scientific Corporation reserves the right to terminate the study at any stage but intends to exercise this right only for valid scientific or business reasons and reasons related to protection of subjects. Investigators, associated IRBs/IECs/HRECs, and regulatory authorities, as applicable, will be notified in writing in the event of study termination.

22.1.1. Criteria for Premature Termination of the Study

Possible reasons for premature study termination include, but are not limited to, the following:

- The occurrence of unanticipated adverse device effects that present a significant or unreasonable risk to subjects enrolled in the study.
- An enrollment rate far below expectation that prejudices the conclusion of the study.
- A decision on the part of BSC to suspend or discontinue development/marketing of the device.

This trial may also be stopped early for effectiveness if upon interim analysis a significant difference in favor of the test arm is observed after enrollment of the first 70% of subjects. Please see Section **11.3.2** for additional information.

22.2. *Termination of Study Participation by the Investigator or Withdrawal of IRB/IEC/HREC Approval*

Any investigator, or associated IRB/IEC/HREC or regulatory authority may discontinue participation in the study or withdraw approval of the study, respectively, with suitable written notice to BSC. Investigators, associated IRBs/IECs/HRECs, and regulatory authorities, as applicable, will be notified in writing in the event of these occurrences.

22.3. *Requirements for Documentation and Subject Follow-up*

In the event of premature study termination, a written statement as to why the premature termination has occurred will be provided to all participating sites by BSC. The IRB/IEC/HREC and regulatory authorities, as applicable, will be notified. Detailed information on how enrolled subjects will be managed thereafter will be provided.

In the event an IRB/IEC/HREC terminates participation in the study, participating investigators, associated IRBs/IECs/HRECs, and regulatory authorities, as applicable, will be notified in writing. Detailed information on how enrolled subjects will be managed thereafter will be provided by BSC.

In the event a Principal Investigator terminates participation in the study, study responsibility will be transferred to another investigator, if possible. In the event there are no opportunities to transfer Principal Investigator responsibility, detailed information on how enrolled subjects will be managed thereafter will be provided by BSC.

The Principal Investigator or his/her designee must return all study-related documents and devices, if supplied by BSC, unless this action would jeopardize the rights, safety, or welfare of the subjects.

22.4. *Criteria for Suspending/Terminating a Study Center*

Boston Scientific Corporation reserves the right to stop the inclusion of subjects at a study center at any time after the study initiation visit if no subjects have been enrolled for a period beyond 3 months after center initiation, or if the center has multiple or severe protocol violations/noncompliance without justification and/or fails to follow remedial actions.

In the event of termination of center participation, all devices and testing equipment, as applicable, will be returned to BSC unless this action would jeopardize the rights, safety or well-being of the subjects. The IRB/IEC/HREC and regulatory authorities, as applicable, will be notified. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

23. Publication Policy

Boston Scientific Corporation requires disclosure of its involvement as a sponsor or financial supporter in any publication or presentation relating to a BSC study or its results. Boston Scientific Corporation 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.

The data, analytic methods, and study materials for this clinical trial may be made available to other researchers in accordance with the Boston Scientific Data Sharing Policy (http://www.bostonscientific.com/).

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25. Abbreviations and Definitions

25.1. *Abbreviations and Acronyms*

Abbreviations and acronyms are shown in **Table 25.1-1**.

Table 25.1-1: Abbreviations and Acronyms

Abbreviation/Acronym	Definition
ADE	adverse device effect
AE	adverse event
AKI	acute kidney injury
BSC	Boston Scientific Corporation
CAM-ICU	Confusion Assessment Method for Intensive Care Unit Patients
CEC	Clinical Events Committee
CEPD	cerebral embolic protection device
eCRF	electronic case report form
EDC	electronic data capture
FLAIR	fluid-attenuated inversion recovery
GCP	Good Clinical Practices
GDPR	General Data Protection Regulation
HREC	Human Research Ethics Committee
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFU	Instructions for Use
IRB	Institutional Review Board
ISO	International Organization for Standardization
ITT	intention to treat
MACCE	major adverse cardiac and cerebrovascular events
MoCA	Montreal Cognitive Assessment
mRS	Modified Rankin Scale
NeuroARC	Neurologic Academic Research Consortium
NIHSS	National Institutes of Health Stroke Scale
SADE	serious adverse device effect
SAE	serious adverse event
SOP	standard operating procedure
TAVR	transcatheter aortic valve replacement
TIA	transient ischemic attack
UADE	unanticipated adverse device effect
USADE	unanticipated serious adverse device effect
VARC	Valve Academic Research Consortium

25.2. *Definitions*

Terms are defined in **Table 25.2-1**. See **Table 25.1-1** for a list of abbreviations.

Table 25.2-1: Definitions

Term	Definition
ACUTE KIDNEY INJURY (AKI) (AKIN System[26])	Change in serum creatinine (up to 7 days) compared to baseline: • Stage 1: Increase in serum creatinine to 150–199% (1.5–1.99 × increase compared with baseline) OR increase of ≥0.3 mg/dl (≥26.4 mmol/L) • Stage 2: Increase in serum creatinine to 200–299% (2.0–2.99 × increase compared with baseline) • Stage 3: Increase in serum creatinine to ≥300% (>3 × increase compared with baseline) OR serum creatinine of ≥4.0 mg/dL (≥354 mmol/L) with an acute increase of at least 0.5 mg/dL (44 mmol/L) -OR- Based on urine output (up to 7 days): • Stage 1: <0.5 ml/kg per hour for >6 but <12 hours • Stage 2: <0.5 ml/kg per hour for >12 but <24 hours • Stage 3: <0.3 ml/kg per hour for ≥24 hours or anuria for ≥12 hours ***Note 1***: Subjects receiving renal replacement therapy are considered to meet Stage 3 criteria irrespective of other criteria.
ACUTE VESSEL OCCLUSION	The state of complete luminal obstruction with no antegrade blood flow
ADVERSE EVENT (AE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, whether or not related to the study medical device. ***Note 1*:** This includes events related to the study medical device or comparator. ***Note 2*:** This definition includes events related to the procedures involved. ***Note 3*:** For users or other persons, this definition is restricted to events related to the study medical device.
ADVERSE DEVICE EFFECT (ADE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Adverse event related to the use of the study medical device ***Note 1*:** This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the study medical device. ***Note 2*:** This definition includes any event resulting from use error or intentional abnormal use of the study medical device.
AORTIC DISSECTION	Intimal tear resulting in blood splitting the aortic media and producing a false lumen that can progress in an antegrade or retrograde direction Aortic dissection is further classified using Stanford classification (Types A and B depending on whether ascending or descending aorta involved) or DeBakey classification (Types I, II and III) [see Figure below].

Table 25.2-1: Definitions

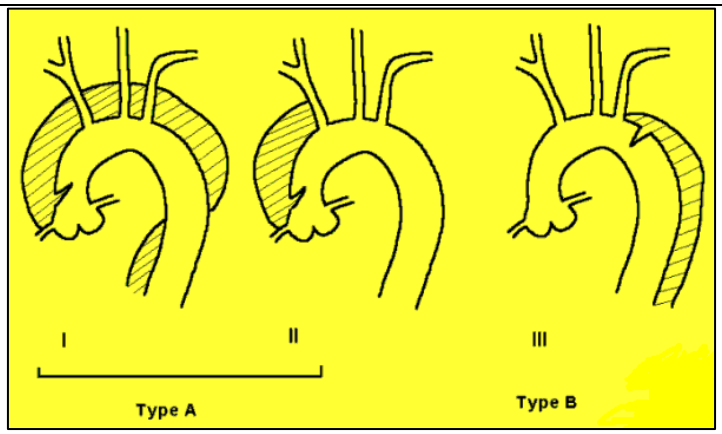
Term	Definition
	
AORTIC REGURGITATION (AR)	The leaking of the aortic valve that causes blood to flow in the reverse direction during ventricular diastole, from the aorta into the left ventricle. The echocardiographic findings in severe aortic regurgitation include the following. • An AR color jet dimension >60% of the left ventricular outflow tract diameter (may not be true if the jet is eccentric) • The pressure half-time of the regurgitant jet is <250 msec • Early termination of the mitral inflow (due to increase in LV pressure due to the AR) • Early diastolic flow reversal in the descending aorta. • Regurgitant volume >60 mL • Regurgitant fraction >55%
ARRHYTHMIA	Any variation from the normal rhythm of the heartbeat, including sinus arrhythmia, premature beat, heart block, atrial fibrillation, atrial flutter and tachycardia. Complete heart block, ventricular tachycardia and ventricular fibrillation are considered major arrhythmias. Data should be collected on any new arrhythmia resulting in hemodynamic instability or requiring therapy (therapy includes electrical/medical cardioversion or initiation of a new medication [oral anticoagulation, rhythm or rate controlling therapy]). New onset atrial fibrillation or atrial flutter (AF) is diagnosed as any arrhythmia within hospitalization that has the ECG characteristics of AF and lasts sufficiently long to be recorded on a 12-lead ECG, or at least 30 seconds on a rhythm strip. The therapeutic approach to new-onset AF (spontaneous conversion, electrical or medical cardioversion, initiation of oral anticoagulation, and rate or rhythm control medications) and any clinical consequences should be documented. ***Note 1***: See also definitions for conductance disturbance and permanent pacemaker.
BLEEDING	<u>Life-threatening or Disabling Bleeding</u> • Fatal bleeding (Bleeding Academic Research Consortium [BARC] type 5[41,42]) • Bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome (BARC type 3b and 3c) • Bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery (BARC type 3b)

Table 25.2-1: Definitions

Term	Definition
	• Overt source of bleeding with drop in hemoglobin of ≥5 g/dL or whole blood or packed red blood cells (RBC) transfusion ≥4 units (BARC type 3b)* <u>Major Bleeding (BARC type 3a)</u> • Overt bleeding either associated with a drop in the hemoglobin level of at least 3.0g/dL or requiring transfusion of 2 or 3 units of whole blood/RBC, or causing hospitalization or permanent injury, or requiring surgery AND does not meet criteria of life-threatening or disabling bleeding <u>Minor Bleeding (BARC type 2 or 3a, depending on the severity)</u> • Any bleeding worthy of clinical mention (e.g., access site hematoma) that does not qualify as life-threatening, disabling, or major * Given one unit of packed RBC typically will raise blood hemoglobin concentration by 1 g/dL, an estimated decrease in hemoglobin will be calculated.
CARDIAC DECOMPENSATION	Inability of the heart to maintain adequate circulation
CARDIAC TAMPONADE	Evidence of a new pericardial effusion associated with hemodynamic instability and clearly related to the TAVR procedure. Clinical syndrome caused by the accumulation of fluid in the pericardial space, resulting in reduced ventricular filling and subsequent hemodynamic compromise.
CARDIOGENIC SHOCK	An insufficient forward cardiac output to maintain adequate perfusion of vital organs to meet ongoing demands for oxygenation and metabolism. Cardiogenic shock is due to either inadequate left ventricular pump function (such as in congestive heart failure) or inadequate left ventricular filling (such as in cardiac tamponade). Cardiogenic shock is defined as sustained hypotension (>30 minutes) with evidence of tissue hypoperfusion including oliguria (<30 mL/h), cool extremities, cyanosis, and altered mental status.
CEREBRAL INFARCTION	Evidence of brain cell death from imaging studies or pathological examination. If there are clinical symptoms, then it is a stroke; otherwise, it is an asymptomatic cerebral infarction.
CHRONIC RENAL INSUFFICIENCY	Subject has chronic impairment of kidney function.
CLINICAL EVENTS COMMITTEE (CEC) EVENT	Includes the following: mortality, stroke/transient ischemic attack, delirium
CONDUCTION DISTURBANCES	Implant-related new or worsened cardiac conduction disturbances include new or worsened first degree atrioventricular (AV) block, second degree AV block (Mobitz I or Mobitz II), third degree AV block, incomplete right bundle branch block (RBBB), RBBB, intraventricular conduction delay, left bundle branch block (LBBB), left anterior fascicular block, or left posterior fascicular block, including block requiring permanent pacemaker implant ***Note 1***: High grade AV block is considered persistent if it is present every time the underlying rhythm is checked. ***Note 2***: See also definitions for arrhythmia and permanent pacemaker.
CONVERSION TO OPEN SURGERY	Conversion to open sternotomy during the TAVR procedure secondary to any procedure-related complications
CORONARY OBSTRUCTION	Angiographic or echocardiographic evidence of a new, partial or complete, obstruction of a coronary ostium, either by the valve prosthesis itself, the native

Table 25.2-1: Definitions

Term	Definition
	leaflets, calcifications, or dissection, occurring during or after the TAVR procedure. Mechanical coronary artery obstruction following TAVR or surgical AVR that typically occurs during the index procedure. Possible mechanisms for mechanical coronary obstruction include the following. • Impingement of the coronary ostia by the valve support structure in the setting of suboptimal valve positioning and/or 'small aortic root' anatomy • Embolization from calcium, thrombus, air, or endocarditis displacement of native aortic valve leaflets towards the coronary ostia during TAVR • Suture-related kinking or obstruction or cannulation related obstruction of the coronary ostia associated with surgical AVR The diagnosis of TAVR-associated coronary obstruction can be determined by imaging studies (coronary angiography, intravascular ultrasound, multi-slice CT angiography, or echocardiography), surgical exploration, or autopsy findings. Cardiac biomarker elevations and ECG changes indicating new ischemia provide corroborative evidence.
DATA CATEGORIES	Data categories as defined by GDPR are listed below. Personal Data: GDPR defines "Personal Data" to be any information relating to an identified or identifiable natural person ('data subject'); an identifiable natural person is one who can be identified, directly or indirectly, in particular by reference to an identifier such as a name, an identification number, location data, an online identifier or to one or more factors specific to the physical, physiological, genetic, mental, economic, cultural or social identity of that natural person. Sensitive Personal Data: GDPR defines "Sensitive Personal Data" as a subset of Personal Data, which, due to their nature have been classified as deserving additional privacy and security protections because their processing may create a risk for an individual's fundamental right and freedom. This subset includes but is not limited to the following: racial, ethnic origin or ethnicity; political opinions; religious or philosophical beliefs; trade union membership; genetic data; biometric data for the purpose of uniquely identifying a natural person; health data (including gender, family medical history, etc.); sex life or sexual orientation; criminal records or allegations of crimes (requires an even higher standard of protection). Identifiers: "Identifiers" are Personal Data that can be used alone or in combination with other identifiers to identify an individual. Identifiers include but are not limited to the following: • All government-issued identification numbers (including but not limited to names, social security number, certificate/license numbers, passport, national ID) • All financial account numbers (including but not limited to bank account numbers, payment numbers, bank or credit card numbers) • All geographic subdivisions smaller than a state, including street address, city, county, precinct, ZIP code, and their equivalent geocodes, except for the initial three digits of the ZIP code if, according to the current publicly available data from the Bureau of the Census, the geographic unit formed by combining all ZIP codes with the same three initial digits contains more than

Table 25.2-1: Definitions

Term	Definition
	20,000 people and/or the initial three digits of a ZIP code for all such geographic units containing 20,000 or fewer people is changed to 000 • All elements of dates (except year) for dates that are directly related to an individual, including birth date, admission date, discharge date, death date, and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older • Telephone numbers • Fax numbers • Device identifiers and serial numbers • E-mail addresses • Web Universal Resource Locators (URLs) • Internet Protocol (IP) addresses • Medical record numbers • Biometric identifiers, including finger and voice prints • Health plan beneficiary numbers • Full-face photographs and any comparable images • Any other unique identifying number, characteristic, or code (including subject ID number)
DEATH	<u>All-cause Death</u> Death from any cause after a valve intervention. <u>Cardiovascular Death</u> Any one of the following criteria is met. • Any death due to proximate cardiac cause (e.g., myocardial infarction, cardiac tamponade, worsening heart failure) • Sudden or unwitnessed death • Death of unknown cause • Death caused by noncoronary vascular conditions such as neurological events, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular disease • All procedure-related deaths, including those related to a complication of the procedure or treatment for a complication of the procedure • All valve-related deaths including structural or nonstructural valve dysfunction or other valve-related adverse events <u>Non-cardiovascular Death</u> • Any death in which the primary cause of death is clearly related to another condition (e.g. trauma, cancer, suicide)
DELIRIUM	Per NeuroARC[21], while multifactorial, delirium (global neurological dysfunction) without central nervous system injury should be adjudicated and reported due to its prognostic implications[43,44]. Assessment tools include the Confusion Assessment Method for ICU Patients (CAM-ICU)[23,24].
DEVICE DEFICIENCY	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. ***Note 1***: Device deficiencies include malfunctions, use errors, and inadequate labeling.

Table 25.2-1: Definitions

Term	Definition
DEVICE FAILURE	A device failure is identified whenever the criteria for device success are not met.
DEVICE MIGRATION	Device migration is defined as an upward or downward displacement of the implanted valve from its original implant location, after initial correct positioning within the aortic annulus from its initial position, with or without consequences. This can be confirmed by X-ray, echocardiography, CT scan or MRI or valve migration demonstrated by direct assessment during open heart surgery or at autopsy.
DEVICE RELATED COMPLICATIONS	Complications associated with the device as it relates to delivery, placement, efficacy or durability; these may involve the implanted device or the delivery system.
DEVICE SUCCESS	Device Success for TAVR as defined by VARC post-implant procedure. VARC 1[22] • Successful vascular access, delivery and deployment of the device and successful retrieval of the delivery system • Correct position of the device in the proper anatomical location • Intended performance of the prosthetic heart valve (aortic valve area >1.2 cm^2 and mean aortic valve gradient <20 mmHg or peak velocity <3 m/s, without moderate or severe prosthetic valve aortic regurgitation) • Only one valve implanted in the proper anatomical location VARC 2[16] • Absence of procedural mortality • Correct positioning of a single transcatheter valve into the proper anatomical location • Intended performance of the Lotus Valve (indexed effective orifice area >0.85 cm^2/m^2 [>0.7 cm^2/m^2 for BMI ≥30 kg/ m^2] plus either a mean aortic valve gradient <20 mm Hg or a peak velocity <3m/sec, without moderate or severe prosthetic valve aortic regurgitation)
ECTOPIC VALVE DEPLOYMENT	Permanent deployment of the valve prosthesis in a location other than the aortic root.
EMBOLISM	Examples include a free-flowing blood clot or lesion material that is located in the systemic or pulmonary circulation. Embolism may be manifested by a neurological event or a noncerebral embolic event.
ENCEPHALOPATHY	Altered mental state (e.g., seizures, delirium, confusion, hallucinations, dementia, coma, psychiatric episode, etc.)
ENDOCARDITIS	**Infective endocarditis** is diagnosed based on Duke criteria[45] and necessitates the following. • Two major criteria -OR- • One major and three minor criteria -OR- • Five minor criteria Major Criteria • Positive blood culture for infective endocarditis o Typical microorganism consistent with infective endocarditis from 2 separate blood cultures, as noted below. ▪ Viridans streptococci, *Streptococcus bovis*, or HACEK group (*Haemophilus* [*Haemophilus parainfluenzae, Haemophilus aphrophilus,*

Table 25.2-1: Definitions

Term	Definition
	and Haemophilus paraphrophilus], *Actinobacillus actinomycetemcomitans* [*Aggregatibacter actinomycetemcomitans*], *Cardiobacterium hominis, Eikenella corrodens, Kingella kingae* -OR- ▪ Community-acquired *Staphylococcus aureus* or enterococci, in the absence of a primary focus -OR- o Microorganisms consistent with infective endocarditis from persistently positive blood cultures defined as noted below. ▪ Two (2) positive cultures of blood samples drawn >12 hours apart -OR- ▪ All of 3 or a majority of 4 separate cultures of blood (with first and last sample drawn 1 hour apart) • Evidence of endocardial involvement o Positive echocardiogram for infective endocarditis defined as noted below. ▪ Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation -OR- ▪ Abscess -OR- ▪ New partial dehiscence of prosthetic valve -OR- o New valvular regurgitation (worsening or changing of preexisting murmur not sufficient) <u>Minor Criteria</u> • Predisposition: predisposing heart condition or intravenous drug use • Fever: temperature >38.0° C (100.4° F) • Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway lesions • Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth spots, and rheumatoid factor • Microbiological evidence: positive blood culture but does not meet a major criterion as noted above or serological evidence of active infection with organism consistent with infective endocarditis • Echocardiographic findings: consistent with infective endocarditis but do not meet a major criterion as noted above **Implanted valve endocarditis** includes any infection involving an implanted valve. The diagnosis of operated valvular endocarditis is based on one of the following criteria. • Fulfillment of the Duke endocarditis criteria as defined above • Evidence of abscess, paravalvular leak, pus, or vegetation confirmed as secondary to infection by histological or bacteriologic studies during a re-operation • Findings of abscess, pus, or vegetation involving a repaired or replaced valve during an autopsy.
EXPLANT	Removal of an investigational valve implant for any reason.
FRAILTY	Slowness, weakness, exhaustion, wasting and malnutrition, poor endurance and inactivity, loss of independence.

Table 25.2-1: Definitions

Term	Definition
GENERAL DATA PROTECTION REGULATION	The General Data Protection Regulation (GDPR) is a legal framework that sets guidelines for the collection and processing of personal information of individuals within the European Union.
HEMOLYSIS	Two plasma free hemoglobin values >40 mg/dL with the two readings taken within a single 48-hour period. If the second plasma free hemoglobin assessment is not performed within 48 hours following an initial determination of >40 mg/dL, this would qualify as an AE.
HOSPITALIZATION DUE TO VALVE-RELATED SYMPTOMS/ WORSENING CONGESTIVE HEART FAILURE	The need for hospitalization associated with valve-related symptoms or worsening CHF (NYHA Class III or IV) is intended to serve as a basis for calculation of a "days alive outside the hospital" endpoint. Included are heart failure, angina, or syncope due to aortic valve disease requiring intervention or intensified medical management; clinical symptoms of CHF with objective signs including pulmonary edema, hypoperfusion, or documented volume overload AND administration of intravenous diuresis or inotropic therapy, performance of aortic valvuloplasty, institution of mechanical support (intra-aortic balloon pump or ventilation for pulmonary edema), or hemodialysis for volume overload; clear documentation of anginal symptoms AND no clinical evidence that angina was related to coronary artery disease or acute coronary syndrome; documented loss of consciousness not related to seizure or tachyarrhythmia.
HOSTILE CHEST	Any of the following or other reasons that make redo operation through sternotomy or right anterior thoracotomy prohibitively hazardous: • Abnormal chest wall anatomy due to severe kyphoscoliosis or other skeletal abnormalities (including thoracoplasty, Potts' disease) • Complications from prior surgery • Evidence of severe radiation damage (e.g. skin burns, bone destruction, muscle loss, lung fibrosis or esophageal stricture) • History of multiple recurrent pleural effusions causing internal adhesions
INTERNAL MAMMARY ARTERY OR OTHER CRITICAL CONDUIT(S) CROSSING MIDLINE AND/OR ADHERENT TO POSTERIOR TABLE OF STERNUM	A patent IMA graft that is adherent to the sternum such that injuring it during reoperation is likely. A patient may be considered extreme risk if any of the following are present: • The conduit(s) are radiographically indistinguishable from the posterior table of the sternum. • The conduit(s) are radiographically distinguishable from the posterior table of the sternum but lie within 2-3mm of the posterior table.
INTRACRANIAL HEMORRHAGE	Collection of blood between the brain and skull; subcategorized as epidural, subdural, and subarachnoid bleeds.

Table 25.2-1: Definitions

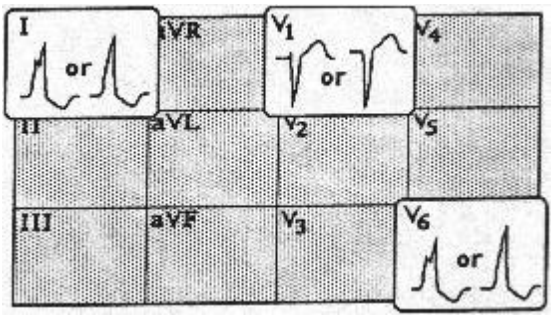
Term	Definition
LEFT BUNDLE BRANCH BLOCK (LBBB)	The appearance of typical complete LBBB in the three KEY leads (I, V1, and V6) with the following diagnostic criteria [see Figure below]. • The heart rhythm must be supraventricular in origin • QRS widening to at least 0.12 sec • An upright (monophasic) QRS complex in leads I and V6; the QRS may be notched, but there should not be any q wave in either lead I or lead V6. • A predominantly negative QRS complex in lead V1; there may or may not be an initial small r wave in lead V1, that is, lead V1 may show either a QS or RS complex. 
LIVER DISEASE (SEVERE) /CIRRHOSIS	Any of the following: • Child-Pugh class C • MELD (Model for End-Stage Liver Disease) score ≥10 • Portal-caval, spleno-renal, or transjugular intrahepatic portal shunt • Biopsy proven cirrhosis with portal hypertension or hepatocellular dysfunction
MITRAL VALVE APPARATUS DAMAGE	Angiographic or echocardiographic evidence of a new damage to the mitral valve apparatus (chordae papillary muscle, or leaflet) during or after the TAVR procedure.
MYOCARDIAL INFARCTION (MI)	**Periprocedural MI (≤72 hours after the index procedure)** • New ischemic symptoms (e.g., chest pain or shortness of breath) or new ischemic signs (e.g., ventricular arrhythmias, new or worsening heart failure, new ST-segment changes, hemodynamic instability, new pathological Q waves in at least two contiguous leads, or imaging evidence of new loss of viable myocardium or new wall motion abnormality) -AND- • Elevated cardiac biomarkers (preferably CK-MB) within 72 h after the index procedure, consisting of at least one sample post-procedure with a peak value exceeding 15× upper reference limit (troponin) or 5× for CK-MB. If cardiac biomarkers are increased at baseline (>99th percentile), a further increase of at least 50% post-procedure is required AND the peak value must exceed the previously stated limit. **Spontaneous MI (>72 hours after the index procedure)** Any one of the following criteria applies. • Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile URL, together with evidence of myocardial ischemia with at least one of the following o Symptoms of ischemia

Table 25.2-1: Definitions

<table>
<tr><th>Term</th><th>Definition</th></tr>
<tr><td></td><td>

o ECG changes indicative of new ischemia [new ST-T changes or new LBBB]
o New pathological Q waves in at least two contiguous leads
o Imaging evidence of new loss of viable myocardium or new wall motion abnormality

Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST-segment elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/ or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.
Pathological findings of an acute myocardial infarction[46].

</td></tr>
<tr><td>NEUROLOGICAL EVENT</td><td>Any central, new neurological deficit, whether temporary or permanent and whether focal or global, that occurs after the subject emerges from anesthesia</td></tr>
<tr><td>NEUROLOGY PROFESSIONAL</td><td>Defined as a neurologist, neurology fellow, neurology physician assistant, or neurology nurse practitioner</td></tr>
<tr><td>NEW YORK HEART ASSOCIATION CLASSIFICATION (NYHA)</td><td>Classification system for defining cardiac disease and related functional limitations into four broad categorizations:
<table>
<tr><td>Class I</td><td>Subject with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.</td></tr>
<tr><td>Class II</td><td>Subjects with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.</td></tr>
<tr><td>Class III</td><td>Subjects with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.</td></tr>
<tr><td>Class IV</td><td>Subjects with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.</td></tr>
</table>
</td></tr>
<tr><td>NONSTRUCTURAL DYSFUNCTION</td><td>Any abnormality not intrinsic to the valve itself that results in stenosis or regurgitation of the operated valve or hemolysis. The term nonstructural dysfunction refers to problems (exclusive of thrombosis and infection) that do not directly involve valve components yet result in dysfunction of an operated valve, as diagnosed by re-operation, autopsy, or clinical investigation. Nonstructural dysfunction includes the following.

Entrapment by pannus, tissue, or suture
Paravalvular leak
Inappropriate sizing or positioning
Residual leak or obstruction after valve implantation or repair
Clinically important intravascular hemolytic anemia
Development of aortic or pulmonic regurgitation as a result of technical errors
Dilatation of the sinotubular junction

</td></tr>
</table>

Table 25.2-1: Definitions

Term	Definition
	• Dilatation of the valve annulus after either valve replacement with stentless prostheses, new onset of coronary ischemia from coronary ostial obstruction, or paravalvular aortic regurgitation
PARAVALVULAR REGURGITATION / PARAVALVULAR LEAK	Leakage due to a separation of the prosthetic valve from the annulus. Any evidence of leakage of blood around the device. Diagnosis of paravalvular regurgitation/paravalvular leak may be obtained from TEE/TTE, however, definitive diagnosis is obtained at re-operation, explant, or autopsy.
PERMANENT PACEMAKER IMPLANTATION (PPI)	Implantation of a new permanent pacemaker after the index procedure resulting from new or worsened conduction disturbances (including new left bundle branch block [LBBB] and third-degree atrioventricular block) • Procedure-related: Permanent pacemaker is implanted in subjects with new onset or worsened conduction disturbances occurring post index procedure • Not related to procedure: Permanent pacemaker is implanted in subjects with known conduction disturbances that did not advance after the index procedure. ***Note***: See also definitions for arrhythmia and conductance disturbance.
PORCELAIN AORTA	Heavy circumferential calcification of the entire ascending aorta extending to the arch such that aortic cross-clamping is not feasible
PROCEDURE RELATED COMPLICATIONS	Complications associated with any part of the vascular access procedure, associated treatments or necessary secondary interventions that do not necessarily involve the device. This includes morbidity associated with either pre-medication, or anesthesia, or other adjunct to the surgical procedure. Other technical errors including inappropriate subject selection, inappropriate operator techniques, measurements, or judgment that do not involve the device itself are also included.
PROCEDURE-RELATED EVENTS	Events occurring during or as a direct result of the index procedure.
REPEAT PROCEDURE FOR VALVE-RELATED DYSFUNCTION	Any surgical or percutaneous interventional catheter procedure that repairs, otherwise alters or adjusts, or replaces a previously implanted valve. In addition to surgical re-operations, balloon dilatation, interventional manipulation, repositioning, or retrieval, and other catheter-based interventions for valve-related complications are also considered reinterventions. Cardiac reinterventions will be categorized as repeat TAVR, valvuloplasty, or surgical AVR.
REPOSITIONING OF A VALVE	Any movement of the valve after the lead in phase (after the posts have entered the buckles)
RESHEATHING OF A VALVE	Full resheathing occurs when the top of the posts re-enter the Lotus catheter during repositioning. Partial resheathing occurs when the posts do not re-enter the Lotus catheter during repositioning.
RESPIRATORY INSUFFICIENCY	Inadequate ventilation or oxygenation
RESPIRATORY FAILURE	The need for ventilatory support for >72 hours associated with an inability to wean from the respirator for any reason.
RIGHT VENTRICULAR INSUFFICIENCY	• Defined as sequelae of right ventricular failure including the following. o Significantly decreased right ventricular systolic and/or diastolic function o Tricuspid valvular regurgitation secondary to elevated pressure • Clinical symptoms to include the following. o Hepatic congestion o Ascites

Table 25.2-1: Definitions

Term	Definition	
	○ Anasarca ○ Presence of "hepato-jugular reflux" ○ Edema Severe right ventricular dysfunction or severe pulmonary hypertension is primary or secondary pulmonary hypertension with PA systolic pressures greater than 2/3 of systemic pressure.	
SERIOUS ADVERSE EVENT (SAE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	***Note 1*:** This definition meets the reporting objectives and requirements of ISO 14155 and MEDDEV 2.7/3. Adverse event that: • Led to death, • Led to serious deterioration in the health of the subject as defined by either: ○ a life-threatening illness or injury, or ○ a permanent impairment of a body structure or a body function, or ○ in-patient hospitalization or prolongation of existing hospitalization, or ○ medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function • Led to fetal distress, fetal death, or a congenital abnormality or birth defect. ***Note 2*:** Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without a serious deterioration in health, is not considered a serious adverse event.	
SERIOUS ADVERSE DEVICE EFFECT (SADE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event	
SOURCE DATA (per ISO 14155:2011)	All information in original records of clinical findings, observations, or other activities in a clinical investigation, necessary for the reconstruction and evaluation of the clinical investigation	
SOURCE DOCUMENT (per ISO 14155:2011)	Printed, optical or electronic document containing source data. Examples: Hospital records, laboratory notes, device accountability records, photograhic negatives, radiographs, records kept at the investigation center, at the laboratories and at the medico-technical departments involvced in the clinical investigation.	
STROKE NeuroARC[21] Neurological Event Definitions	**Type**	**Description**
	Type 1 − Overt CNS Injury: Acutely Symptomatic Brain or Spinal Cord Injury	
	Type 1.a Ischemic stroke	Sudden onset of neurological signs or symptoms fitting a focal or multifocal vascular territory within the brain, spinal cord, or retina, that: 1. Persist for ≥24 h or until death, with pathology or neuroimaging evidence that demonstrates either: a. CNS infarction in the corresponding vascular territory (with or without hemorrhage); or b. Absence of other apparent causes (including hemorrhage), even if no evidence of acute ischemia in the corresponding vascular territory is detected *or*

Table 25.2-1: Definitions

Term	Definition	
		2. Symptoms lasting <24 h, with pathology or neuroimaging confirmation of CNS infarction in the corresponding vascular territory. *Note:* When CNS infarction location does not match the transient symptoms, the event would be classified as covert CNS infarction (Type 2a) and a TIA (Type 3a), but not as an ischemic stroke. Signs and symptoms consistent with stroke typically include an acute onset of 1 of the following: focal weakness and/or numbness; impaired language production or comprehension; homonymous hemianopia or quadrantanopsia; diplopia; altitudinal monocular blindness; hemispatial neglect; dysarthria; vertigo; or ataxia.
	Type 2 − Covert CNS Injury: Acutely Asymptomatic Brain or Spinal Cord Injury Detected by Neuroimaging	
	Type 2.a Covert CNS infarction	Brain, spinal cord, or retinal cell death attributable to focal or multifocal ischemia, on the basis of neuroimaging or pathological evidence of CNS infarction, without a history of acute neurological symptoms consistent with the lesion location
	Subtype 2.a.H Covert CNS infarction with hemorrhagic conversion	Covert CNS infarction includes hemorrhagic conversions. These should be subclassified as Class A or B when CNS infarction is the primary mechanism and neuroimaging or pathology confirms a hemorrhagic conversion. Class A: Petechial hemorrhage: Petechiae or confluent petechiae within the infarction or its margins, but without a space-occupying effect Class B: Confluent hemorrhage: Confluent hemorrhage originating from within the infarcted area with a space-occupying effect
	Type 2.b Covert CNS hemorrhage	Neuroimaging or pathological evidence of CNS hemorrhage within the brain parenchyma, subarachnoid space, ventricular system, spinal cord, or retina on neuroimaging that is not caused by trauma, without a history of acute neurological symptoms consistent with the bleeding location.
	Type 3 – Neurological Dysfunction (Acutely Symptomatic) Without CNS Injury	
	Type 3.a Transient ischemic attack	Transient focal neurological signs or symptoms (lasting <24 h) presumed to be due to focal brain, spinal cord, or retinal ischemia, but without evidence of acute infarction by neuroimaging or pathology (or in the absence of imaging).
	Type 3.b Delirium without CNS injury	Transient nonfocal (global) neurological signs or symptoms (variable duration) without evidence of cell death by neuroimaging or pathology.
	Composite Neurological Endpoints[a]	
	CNS infarction	Any brain, spinal cord, or retinal infarction on the basis of imaging, pathology, or clinical symptoms persisting for ≥24 h (includes Types 1.a, 1.a.H, 1.d, 1.e, 2.a, 2.a.H)
	CNS hemorrhage	Any brain, spinal cord, or retinal hemorrhage on the basis of imaging or pathology, not caused by trauma (includes Type 1.b,

Table 25.2-1: Definitions

Term	Definition
	1.c, 2.b)
	a: Neurological endpoints are not mutually exclusive; an individual subject may have >1 event. VARC–defined stroke includes all Type 1 events (stroke and symptomatic hypoxic-ischemic injury). American Stroke Association–defined stroke includes Type 1.a–d events (overt [focal only] CNS injury), and Type 2.a and 2.a.H (covert CNS infarction).
STROKE VARC[16,22]	Stroke is defined as an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction **Stroke Classification** • Ischemic Stroke is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by an infarction of central nervous system tissue. • Hemorrhagic Stroke is defined as an acute episode of focal or global cerebral or spinal dysfunction caused by an intraparenchymal, intraventricular, or subarachnoid hemorrhage ***Note 1***: The CEC will adjudicate ischemic versus hemorrhagic stroke. ***Note 2***: A stroke may be classified as undetermined if there is insufficient information to allow categorization as ischemic or hemorrhagic **Stroke Diagnostic Criteria** • Rapid onset of a focal or global neurological deficit with at least one of the following: change in level of consciousness, hemiplegia, hemiparesis, numbness or sensory loss affecting one side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke • Duration of a focal or global neurological deficit ≥24 h; OR <24 h, if available neuroimaging documents a new hemorrhage or infarct; OR the neurological deficit results in death • No other readily identifiable nonstroke cause for the clinical presentation (e.g., brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences), to be determined by or in conjunction with designated neurologist • Confirmation of the diagnosis by at least one of the following. o Neurology or neurosurgical specialist o Neuroimaging procedure (MRI or CT scan), but stroke may be diagnosed on clinical grounds alone ***Note 3***: Subjects with non-focal global encephalopathy will not be reported as a stroke without unequivocal evidence based upon neuroimaging studies (CT scan or brain MRI). **Stroke Definitions** Diagnosis as above, preferably with positive neuroimaging study • Non-disabling: Modified Rankin Scale (mRS) score <2 at 90 days OR one that does not result in an increase of at least one mRS category from an individual's pre-stroke baseline • Disabling: Modified Rankin Scale score ≥2 at 90 days AND an increase of at least one mRS category from an individual's pre-stroke baseline ***Note 4***: Modified Rankin Scale assessments should be made by qualified individuals according to a certification process.

Table 25.2-1: Definitions

Term	Definition
	Note 5: Assessment of the mRS score should occur at baseline; mRS also should be performed after a stroke and at 90 days after the onset of any stroke.
STRUCTURAL VALVE DETERIORATION (SVD)	Component of time-related valve safety defined as follows. • Valve-related dysfunction: Mean aortic valve gradient ≥20 mmHg, EOA ≤0.9-1.1 cm^2, and/or DVI <0.35 AND/OR moderate or severe prosthetic valve regurgitation (per VARC definition) • Requiring repeat procedure (TAVR or SAVR). ***Note:*** Additional outcomes may be measured per definitions set in the most current VARC guidelines (as released at the time of analysis).
SURGICAL RISK[47]	Surgical risk is determined by the Heart Team, including a center cardiac surgeon. ***Note:*** Input from the Heart Team regarding anatomic or functional factors not reflected in the Society of Thoracic Surgeons predicted risk of mortality (STS-PROM) score may increase patient risk above the definitions provided below. **Extreme Risk**: Predicted operative mortality risk ≥15% at 30 days as determined by STS-PROM score **High Risk**: Predicted operative mortality risk ≥8% at 30 days as determined by STS-PROM score **Intermediate Risk**: Predicted operative mortality risk ≥3% and <8% at 30 days as determined by STS-PROM score **Low Risk**: Predicted operative mortality risk <3% at 30 days as determined by STS-PROM score
TAV-IN-TAV DEPLOYMENT	An additional valve prosthesis is implanted within a previously implanted prosthesis because of suboptimal device position and/or function during or after the index procedure.
TRANSIENT ISCHEMIC ATTACK (TIA)	• Transient episode of focal neurological dysfunction caused by brain, spinal cord, or retinal ischemia, without acute infarction • Duration of a focal or global neurological deficit is <24 h • Neuroimaging does not demonstrate a new hemorrhage or infarct (if performed) ***Note***: The difference between TIA and ischemic stroke is the presence of tissue damage or new sensory-motor deficit persisting >24 hours. By definition, TIA does not produce lasting disability.
UNANTICIPATED ADVERSE DEVICE EFFECT (UADE) *Ref: 21 CFR Part 812*	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 subjects.
UNANTICIPATED SERIOUS ADVERSE DEVICE EFFECT (USADE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report ***Note***: An anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity, or outcome has been identified in the risk analysis report.
UNPLANNED USE OF CPB	Unplanned use of cardiopulmonary bypass (CPB) for hemodynamic support at any time during the TAVR procedure

Table 25.2-1: Definitions

Term	Definition
VALVE EMBOLIZATION	The valve prosthesis moves during or after deployment such that it loses contact with the aortic annulus.
VALVE MALAPPOSITION	Includes valve migration, valve embolization, ectopic valve deployment, or transcatheter aortic valve (TAV)-in-TAV deployment.
VALVE MIGRATION	After initial correct positioning the valve prosthesis moves upward or downward within the aortic annulus from its initial position, with or without consequences (e.g., regurgitation).
VALVE-RELATED DYSFUNCTION	Mean aortic valve gradient ≥20 mmHg, EOA ≤0.9-1.1 cm^2, and/or DVI <0.35 AND/OR moderate or severe prosthetic valve aortic regurgitation (per VARC definition)
VALVE THROMBOSIS	Any thrombus attached to or near an implanted valve that occludes part of the blood flow path, interferes with valve function, or is sufficiently large to warrant treatment. Note that valve-associated thrombus identified at autopsy in a patient whose cause of death was not valve-related or at operation for an unrelated indication should not be reported as valve thrombosis.

Table 25.2-1: Definitions

Term	Definition
VASCULAR ACCESS SITE AND ACCESS RELATED COMPLICATIONS	**Major Vascular Complications** • Any aortic dissection, aortic rupture, annulus rupture, left ventricle perforation, or new apical aneurysm/pseudoaneurysm • Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, hematoma, irreversible nerve injury, compartment syndrome, percutaneous closure device failure*) ***leading to*** death, life-threatening or major bleeding**, visceral ischaemia, or neurological impairment • Distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage • The use of unplanned endovascular or surgical intervention ***associated*** with death, major bleeding, visceral ischaemia or neurological impairment • Any new ipsilateral lower extremity ischemia documented by patient symptoms, physical exam, and/or decreased or absent blood flow on lower extremity angiogram • Surgery for access site-related nerve injury • Permanent access site-related nerve injury **Minor Vascular Complications** • Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysms, hematomas, percutaneous closure device failure*) not leading to death, life-threatening or major bleeding**, visceral ischaemia or neurological impairment • Distal embolization treated with embolectomy and/or thrombectomy and not resulting in amputation or irreversible end-organ damage • Any unplanned endovascular stenting or unplanned surgical intervention not meeting the criteria for a major vascular complication • Vascular repair or the need for vascular repair (via surgery, ultrasound-guided compression, transcatheter embolization, or stent-graft) ***Percutaneous Closure Device Failure** Failure of a closure device to achieve hemostasis at the arteriotomy site leading to alternative treatment (other than manual compression or adjunctive endovascular ballooning) ***Note 1*:** Pre-planned surgical access or a planned endovascular approach to vascular closure (e.g., "pre-closure")[48,49] should be considered as part of the TAVR procedure and not as a complication, unless untoward clinical consequences are documented (e.g., bleeding complications, limb ischemia, distal embolization, or neurological impairment). ***Note 2***: If unplanned percutaneous or surgical intervention does not lead to adverse outcomes this is not considered a major vascular complication. ** Refers to VARC bleeding definitions
VENTRICULAR SEPTAL PERFORATION	Angiographic or echocardiographic evidence of a new septal perforation during or after the TAVR procedure
VESSEL PERFORATION	Unexpected puncture of the vessel with evidence of extravasation into extraluminal surrounding tissue or space requiring treatment using interventional or surgical techniques

Abbreviations: ADE=adverse device effect; AE=adverse event; AR=aortic regurgitation; AVA=aortic valve area; AVR= aortic valve replacement; CEC=Clinical Events Committee; CK=creatine kinase; CNS=central

Table 25.2-1: Definitions

Term	Definition
nervous system; CT=computed tomography; DVI=Doppler velocity index; ECG=electrocardiogram; EOA=effective orifice area; FEV=forced expiratory volume; GDPR=General Data Protection Regulation; LBBB=left bundle branch block; LV=left ventricle; MI=myocardial infarction; MRI=magnetic resonance imaging; NeuroARC=Neurologic Academic Research Consortium; NYHA=New York Heart Association; PPI=permanent pacemaker implant; RBC=red blood cell; SADE=serious adverse device effect; SAE=serious adverse event; SVD=structural valve deterioration; TAVR =transcatheter aortic valve replacement; TEE=transesophageal Doppler echocardiography; TIA=transient ischemic attack; USADE= unanticipated serious adverse device effect; URL=upper reference limit (defined as 99th percentile of normal reference range); VARC=Valve Academic Research Consortium	