RESPOND: Repositionable Lotus Valve **S**ystem – **Po**st Market Evaluatio**n** of Real Worl**d** Clinical Outcomes

CLINICAL STUDY PROTOCOL

Protocol Number: TP6461

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2. Protocol Synopsis

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Objective(s)	To collect real world clinical and device performance outcomes data with the Lotus™ Valve System used in routine clinical practice for the treatment of severe calcific aortic stenosis.
Indication(s) for Use	The Lotus Valve System is indicated to improve aortic valve function for symptomatic subjects with severe calcific aortic stenosis (aortic valve area [AVA] of <1.0 cm^2 or index of <0.6 cm^2/m^2) who are at high risk for standard surgical valve replacement.
Test Device	Commercially available Lotus Valve Systems.
Study Design	A prospective, open label, single arm, multi-center, observational post market study. Study cohorts include the main cohort of approximately 1000 subjects and a second cohort of approximately 80 subjects.
Planned Number of Subjects	The main cohort of approximately 1000 real-world, prospective, consecutive subjects will be enrolled at up to 60 study centers in Europe, Asia Pacific and South America. An additional cohort of approximately 80 subjects will be enrolled at up to 8 study centers in Europe after enrollment in the main cohort is completed to assess center-driven implantation technique with the commercially available Lotus Valve System. NOTE: Consecutive is defined as a commitment by the participating investigators at each study center to enroll all consented patients admitted for transcatheter aortic valve implantation (TAVI) who are selected to receive a Lotus Valve.
Study Population	All subjects who are candidates for transcatheter aortic valve implantation (TAVI), signed the Informed Consent Form (ICF) and are selected to receive a Lotus Valve will be evaluated for enrollment in this study
Definition of Enrollment	A subject is considered enrolled upon obtaining a signed ICF from the subject or subject's legally authorized representative (LAR) and an attempt to insert the Lotus Introducer sheath.
Primary Endpoint	Main cohort: All-cause mortality at 30 days and 1 year after the implant procedure. All-cause mortality at 30 days will be compared to a pre-specified performance goal.

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	Additional cohort: All-cause mortality at 30 days after the implant procedure.

Secondary Endpoints	The following secondary endpoints will be assessed according to current Valve Academic Research Consortium (VARC) guidelines:
	• Safety composite of all-cause mortality and disabling stroke at 30 days and 1 year
	• In-hospital mortality
	• The VARC efficacy composite at 1 year, including all-cause mortality (after 30 days); all stroke (disabling and non-disabling); re-hospitalization for valve-related symptoms or worsening congestive heart failure (NYHA class III or IV); and prosthetic valve-related dysfunction (mean aortic valve gradient ≥20 mmHg, effective orifice area (EOA) ≤0.9–1.1 cm^2 and/or Doppler velocity index (DVI) <0.35 m/s, AND/OR moderate or severe prosthetic valve aortic regurgitation)
	• Time related valve safety composite at 1 year, including structural valve deterioration (valve-related dysfunction requiring repeat procedure [TAVI or SAVR]); prosthetic valve endocarditis; prosthetic valve thrombosis; thromboembolic events (e.g. stroke) and VARC bleeding, unless clearly unrelated to valve therapy based on investigator assessment (e.g. trauma)
	• Clinical endpoints at 30 days defined according to current VARC guidelines:
	  ○ Life-threatening bleeding
	  ○ Acute kidney injury—Stage 2 or 3 (including renal replacement therapy)
	  ○ Coronary artery obstruction requiring intervention
	  ○ Major vascular complication
	  ○ Valve-related dysfunction requiring repeat procedure (BAV, TAVI, or SAVR)
	  ○ New conduction disturbances (LBBB, AVB, RBBB) and need for permanent pacemaker implantation
	• Grade of paravalvular aortic valve regurgitation pre-discharge as measured by transthoracic echocardiography (TTE) and assessed by an independent core laboratory. The moderate and severe paravalvular aortic regurgitation rate will be compared to a pre-specified performance goal.
	NOTE: Secondary endpoints will be assessed in the additional cohort of 80 patients through 30 day follow up.

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Additional Measurements	• The following events at discharge will be collected based on the current VARC definitions[a,b]: o All-cause death (cardiovascular and non-cardiovascular) o Stroke: disabling and non-disabling o Myocardial infarction (MI): periprocedural (≤72 hours post index procedure) and spontaneous (>72 hours post index procedure) o Bleeding: life-threatening (or disabling), major and minor o Acute kidney injury (≤7 days post index procedure): based on the AKIN System Stage 3 (including renal replacement therapy), Stage 2, and Stage 1 o Major and minor vascular complication o Repeat procedure for valve-related dysfunction (surgical or interventional therapy) o Hospitalization for valve-related symptoms or worsening congestive heart failure (NYHA class III or IV) o New permanent pacemaker implantation resulting from new or worsened conduction disturbances (including new left bundle branch block [LBBB] and third degree atrioventricular block) o New onset of atrial fibrillation or atrial flutter o Coronary obstruction (periprocedural) o Ventricular septal perforation (periprocedural) o Mitral apparatus damage (periprocedural) o Cardiac tamponade (periprocedural) o Prosthetic aortic valve malapposition, including valve migration, valve embolization, ectopic valve deployment, or transcatheter aortic valve (TAV)-in-TAV deployment o Prosthetic aortic valve thrombosis o Prosthetic aortic valve endocarditis • Device performance measured peri- and post-procedurally consisting of the following: o Successful vascular access, delivery and deployment of the Lotus Valve System, and successful retrieval of the delivery system o Successful repositioning (partial or complete resheathing of the Lotus Valve in the catheter and redeployment in a more accurate position within the aortic valve annulus) of the Lotus

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	Valve System if repositioning is attempted o Successful retrieval (complete resheathing of the Lotus Valve in the catheter and removal from the body) of the Lotus Valve System if retrieval is attempted o Grade of paravalvular aortic valve regurgitation • Physicians Preference Test (PPT), including device deficiencies, to measure device usability and ease of use peri-procedurally. • Prosthetic aortic valve performance as measured by transthoracic echocardiography (TTE) and assessed by an independent core laboratory, including effective orifice area, mean and peak aortic gradients, peak aortic velocity, and grade of aortic regurgitation, pre-discharge and at 1 year. Site reported TTE measures will be collected at 30 days and annually from 2 through 5 year follow up per local standard of care for TAVI. • Health status as evaluated by EuroQoL (EQ-5D) Quality of Life questionnaire at baseline, 30 days, 1, 3 and 5 year follow up, during in-person clinic visit or via postal mail. • New York Heart Association (NYHA) functional classification at baseline, discharge, 30 days, 1 year and annually through 5 year follow up. [a] Kappetein AP, *et al. J Am Coll Cardiol.* 2012;60:1438-1454 [b] Leon M, *et al. J Am Coll Cardiol.* 2011;57:253-269 NOTE: Additional measurements will be assessed in the additional cohort of 80 patients through 30 day follow up.
Safety Parameters	• Any serious adverse event (SAE) that led to death, serious adverse device effect (SADE), adverse device effect (ADE), unanticipated serious adverse device effect (USADE), and VARC event regardless of seriousness and device relationship will be collected through complete subject follow up. • All-cause mortality and stroke events will be adjudicated by an independent Clinical Events Committee (CEC) through complete subject follow up. • Reporting of device deficiencies will follow applicable regional post-market safety surveillance requirements.
Follow-up Schedule	For the main cohort of 1000 subjects, follow up will occur at 30 days and 1, 2, 3, 4 and 5 years post index valve implantation for all enrolled subjects. Follow-up visit at 1 year post valve implantation

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	should be conducted via outpatient clinic visit. Follow up visits at 30 days and 2 through 5 years may be conducted in person (preferred) or via telephone interview. For the additional cohort of 80 subjects, which is designed to evaluate center-driven implant technique, follow up will occur at 30 days post index valve implantation for all enrolled subjects. Subjects who are not implanted with a Lotus Valve will be followed for safety through 30 days after the initial attempted index procedure.
Statistical Methods	
Statistical Method for the Primary Endpoint (Main Cohort)	All-cause mortality at 30 days post implant procedure is less than a performance goal (PG) of 14% (expected rate of 10% + testing margin of 4%). A one-sample exact binominal test will be used to test the one-sided hypothesis: H_0: $Mortality_{30D} \geq PG$ H_1: $Mortality_{30D} < PG$ where $Mortality_{30D}$ is the 30-day all-cause mortality rate for the Lotus Valve and PG is 14%.
Sample Size Parameters (Main Cohort)	• Expected 30-day all-cause mortality rate = 10% • Performance goal (PG) = 14% (expected rate of 10% + testing margin of 4%) • Test significance level (α) = 0.025 (1-sided) • Power ($1 - \beta$) > 95% • Planned enrollment of up to 1000 subjects • Two planned interim analyses on the primary endpoint at 30 days post-implant procedure will be performed on the first 250 and 500 subjects enrolled. A final analysis will be performed on all enrolled subjects • The primary analysis population for the primary endpoint will be the subject population attempted or implanted with the Lotus Valve. ***Note***: The expected 30-day all-cause mortality rate is assumed to be 10% based on a literature review of studies evaluating the Medtronic CoreValve System and the Edwards Lifesciences SAPIEN Transcatheter Heart Valve System (FRANCE 2 registry[a]). ***Note*:** The alpha-level for the interim and final analyses is adjusted using

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	the Pocock alpha spending function (see Success Criteria below). [a] Gilard M, et al. *N Engl J Med* 2012;366:1705
Statistical Method for the Secondary Endpoint (Main Cohort)	Proportion of subjects with moderate/severe aortic regurgitation pre-discharge as assessed by TTE post implant procedure is less than the PG of 16.5%. A one-sample exact binominal test will be used to test the one-sided hypothesis: H_0: $AR_{pre\text{-}discharge} \geq PG$ H_1: $AR_{pre\text{-}discharge} < PG$ where $AR_{pre\text{-}discharge}$ is the proportion of subjects with moderate/severe aortic regurgitation pre-discharge as assessed by TTE post implant procedure for the Lotus Valve and PG is 16.5%.
Sample Size Parameters (Main Cohort)	• Expected proportion of subjects with moderate/severe aortic regurgitation pre-discharge as assessed by TTE post implant procedure = 10% • Performance goal (PG) = 16.5% (based on FRANCE 2 registry) • Test significance level (α) = 0.025 (1-sided) • Power ($1 - \beta$) > 99% • Planned enrollment of up to 1000 subjects • Two planned interim analyses on the secondary endpoint prior to discharge from the hospital post- implant procedure will be performed on the first 250 and 500 subjects enrolled. A final analysis will be performed on all enrolled subjects • The primary analysis population for the secondary endpoint will be the subject population implanted with the Lotus Valve. ***Note***: The performance goal is set at 16.5% based on rates observed with Medtronic CoreValve System and the Edwards Lifesciences SAPIEN Transcatheter Heart Valve System (FRANCE 2 registry). ***Note*:** The alpha-level for the interim and final analyses is adjusted using the Pocock alpha spending function (see Success Criteria below).
Success Criteria (Main Cohort)	Two interim analyses for the primary and secondary endpoints will be conducted on the first 250 and 500 subjects and a final analysis will be conducted on the planned 1000 subjects. The Pocock alpha spending[a] function is used to adjust the alpha-level for each analysis: 0.00894, 0.00895, and 0.01301, respectively. If the *P* value from the one-sample

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	exact binominal test is <alpha, the Lotus Valve will be concluded to have event rate < PG. This corresponds to the one-sided Clopper-Pearson upper (1-alpha)% confidence bound of the observed event rate being < PG. The data of the additional cohort of approximately 80 subjects will be summarized using descriptive statistics and will not be pooled with the first cohort of 1,000 subjects in the data analysis. No statistical hypotheses will be tested in the additional cohort. [a] Kim K, DeMets DL. *Biometrika* 1987;74:149

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4. Introduction

The incidence of aortic stenosis (AS) is increasing due to the aging of the world-wide population and the lack of drug therapies to prevent, halt, or effectively slow the stenotic process[1,2]. Nearly 5% of individuals >75 years of age have some degree of AS[1,2]. Once symptoms manifest, the prognosis is poor, especially when associated with congestive heart failure. Successful treatment of aortic valve obstruction can result in the improvement of symptoms, hemodynamic parameters, systolic function, and cardiac hypertrophy along with increased survival.

Surgical aortic valve replacement (SAVR) remains the gold standard treatment for the management of subjects with severe AS. However, the operative risk is increased in elderly subjects, in subjects with concomitant coronary artery disease or severely reduced left ventricular (LV) function, and in subjects with associated comorbidities such as cerebral and peripheral vascular disease, renal failure, and respiratory dysfunction[3-5]. Percutaneous transluminal aortic valvuloplasty, which was introduced as an alternative to SAVR in elderly and/or high-risk subjects, can provide symptomatic relief and/or temporary improvement but does not provide definitive treatment in subjects with severe calcified AS. It is also associated with relatively high mortality and complication rates[6].

Transcatheter aortic valve implantation (TAVI) has recently emerged as an alternative to the surgical approach in the treatment of severe AS in subjects who are not suitable candidates for open-heart surgery[7]. This technology is generally restricted to subjects considered at prohibitive or high surgical risk. Evidence of the safety of the procedure using either a balloon expandable or a self-expanding bioprosthetic heart valve has rapidly accumulated through observational studies[8-19], device-specific registries[20-31], national registries[32-38], and randomized controlled trials[39-42]. An expert consensus document on TAVI was recently published[43]. Standardized endpoint definitions were published by the Valve Academic Research Consortium (VARC) in 2011 and updated in 2012[44,45].

The RESPOND study is designed to provide post-market surveillance information on the Lotus™ Valve System after it has placed on the market of the European Economic Area and other regions worldwide. The study will collect clinical and device performance outcomes data for patients receiving the Lotus Valve System over 5 years in a real world setting.

The Lotus Valve System consists of a pre-loaded, stent-mounted tissue valve prosthesis and catheter delivery system designed to enable predictable and precise placement of the valve during TAVI[46]. Early leaflet function during valve deployment and the presence of a radiopaque tantalum marker on the braided frame facilitates optimal initial positioning of the valve. If needed, the valve may be un-locked after being locked and partially or fully re-sheathed for repositioning prior to final release or can be fully retrieved if during the procedure the decision is made not to implant. The valve also has a polycarbonate-based urethane outer seal (Adaptive™ Seal) designed to minimize paravalvular leakage. Additional device information can be found in Section 5.

The Lotus Valve is currently under study in the REPRISE Clinical Program to evaluate the safety and performance of the Lotus Valve System for TAVI in symptomatic subjects with severe calcific aortic stenosis who are considered high risk for surgical valve replacement.

4.1. *REPRISE I*

The REPRISE I clinical study is a prospective, single arm, multicenter feasibility study designed to assess the acute safety and performance of the Lotus Valve System in symptomatic subjects (N=11) with calcified stenotic aortic valves who were considered high risk for surgical valve replacement.

4.1.1. Primary Endpoint

The primary endpoint was clinical procedural success, defined as successful implantation of a Lotus Valve (per the Valve Academic Research Consortium [VARC] definitions) without in-hospital major adverse cardiovascular and cerebrovascular events (MACCE, defined as all-cause mortality, periprocedural myocardial infarction ≤72 hours after the index procedure, major stroke, urgent/emergent conversion to surgery or repeat procedure for valve-related dysfunction) through discharge or 7 days post-procedure, whichever came first. Clinical follow-up will extend through 5 years.

Table 4-1 summarizes primary endpoint data as adjudicated by a CEC. The primary endpoint was achieved in 9/11 subjects. The device was successfully implanted in all 11 subjects but there was a device failure in 1 subject based on not meeting one of four VARC-1 criteria[44] for device success. The Echocardiography Core Lab concluded that the device failure (mean aortic valve gradient >20 mmHg) resulted from a hyperdynamic state in the subject and noted that the prosthetic valve appeared to be functioning well. Ten (10) of 11 subjects had no in-hospital MACCE; there were no deaths and 1 major stroke through discharge.

Table 4-1: REPRISE I Primary Endpoint

Variable	REPRISE I (N=11)
Clinical procedural success	81.8% (9/11)
Device success	90.9% (10/11)
Successful vascular access, delivery and deployment of the device and successful retrieval of the delivery system with correct position of the device in the proper anatomical location – at Procedure	100% (11/11)
Intended performance of the Lotus Valve (AVA >1.0 cm^2 plus either a mean aortic valve gradient <20 mmHg or peak velocity <3m/sec, without moderate or severe prosthetic valve aortic regurgitation) – at Discharge	90.9% (10/11)
Only one valve implanted in the proper anatomical location – at Procedure	100% (11/11)
No in-hospital MACCE through Discharge	90.9% (10/11)

Numbers are % (count/sample size).
"Discharge" represents discharge from hospitalization or 7 days post-procedure, whichever comes first.
Abbreviations: AVA= aortic valve area; MACCE=major adverse cardiovascular and cerebrovascular events

4.1.2. Secondary Endpoints

Secondary endpoints include procedural device performance endpoints as determined by the investigator and echocardiography core lab analyses and are shown in Table 4-2. All attempts to reposition the Lotus Valve were successful (4/4) and retrieval of the valve was not required/attempted in any subject. Core lab adjudication of AR after valve placement indicated 2 cases of mild and 1 case of trivial paravalvular regurgitation; there was no paravalvular regurgitation in 8/11 cases. The single case of central/commissural regurgitation was considered trivial. Additional echocardiography data are presented below.

Table 4-2: REPRISE I Secondary Endpoints

Variable	REPRISE I (N=11)
Successful repositioning of the Lotus Valve System, if attempted	100% (4/4)
Successful retrieval of the Lotus Valve System, if attempted	Not applicable
Incidence of aortic valve regurgitation at Discharge (Core Lab determination)	
Central/commissural regurgitation	9.1% (1/11)
Trivial	9.1% (1/11)
Mild	0.0% (0/11)
Moderate	0.0% (0/11)
Severe	0.0% (0/11)
Paravalvular regurgitation	27.3% (3/11)
Trivial	9.1% (1/11)
Mild	18.2% (2/11)
Moderate	0.0% (0/11)
Severe	0.0% (0/11)

Numbers are % (count/sample size).
"Discharge" represents discharge from hospitalization or 7 days post-procedure, whichever comes first.

To date, data are available through 1 year[47]. There were no additional MACCE events beyond the primary endpoint. While all REPRISE I subjects were NYHA Class II (n=6) or Class III (n=5) at baseline, this distribution was significantly improved at 1 year (5 in Class I, 6 in Class II, 0 in Class III; *P*=0.004). The mean aortic valve gradient was 15.4±4.6 mmHg for the cohort at 1 year, which was below the VARC criterion of 20 mmHg, and there was no moderate or severe paravalvular aortic regurgitation.

4.1.3. Conclusion

The results of the REPRISE I feasibility study support the acute safety and performance of the Lotus Valve System.

4.2. *REPRISE II*

The REPRISE II clinical study is a prospective, single-arm, multicenter study designed to evaluate the safety and performance of the Lotus Valve System for TAVI in symptomatic subjects who have severe calcific aortic valve stenosis and who are at high risk for surgical aortic valve replacement (SAVR).

A total of up to 120 subjects were enrolled in the main study at up to 15 centers Europe and Asia Pacific regions. Subsequently, up to 130 additional subjects will be enrolled at up to 21 centers in the extended trial cohort in Europe and Asia Pacific regions. All subjects implanted will be followed at baseline, peri- and post-procedure, at discharge or 7 days post-procedure (whichever comes first), 30 days, 3 months, 6 months, and then annually for up to 5 years post-procedure.

4.2.1. Primary Endpoint

4.2.1.1. Primary Device Performance Endpoint

Primary Device Performance Endpoint is mean aortic valve pressure gradient at 30 days post implant procedure as measured by echocardiography and assessed by an independent core laboratory.

For the pre-specified interim analysis of the 60-subject cohort, the 30-day mean aortic valve pressure gradient was 11.28±5.23 mmHg with a one-sided 99.208% upper confidence bound of 13.09 (Table 4-3). The *P* value from the one-sample *t*-test was <0.0001, which is below the threshold value of 0.00792. Thus, the Lotus Valve was concluded to have a 30-day mean aortic pressure gradient <18 mmHg and the primary device performance endpoint was met[48].

Table 4-3: REPRISE II Primary Device Performance Endpoint, As-Treated Analysis Set (N=60)

Measure	REPRISE II (N=60)	[95% Confidence Interval]	One-sided Upper Confidence Bound[a]	Performance Goal	One-sided *P* value[b]
30-Day mean aortic valve pressure gradient	11.28±5.23 (52) (4.50, 31.00)	[9.86, 12.70]	13.09	18.00	<0.0001

a: From *t*-test
b: From one-sample *t*-test

4.2.1.2. Primary Safety Endpoint

Primary Safety Endpoint is all-cause mortality at 30 days post implant procedure. For the 60-subject cohort, the primary safety endpoint, all-cause mortality at 30 days, was 1.7%.

4.2.2. Secondary Endpoints

Secondary endpoints are shown in Table 4-4. Successful vascular access, delivery and deployment of the Lotus Valve along with successful retrieval of the delivery system was achieved in all subjects (60/60). All attempts to reposition the Lotus Valve were successful

(16/16) as were all attempts to retrieve the Lotus Valve (4/4). The composite device success endpoint (VARC 2 definition[45]) was 54.5% (24/44). This low rate of success was driven by the low number of subjects meeting the indexed EOA criteria (>0.85 cm^2/m^2 [>0.7 cm^2/m^2 for BMI ≥30 kg/m^2]), which was 60.5% (26/43) in REPRISE II. This value is similar to what has been reported in the PARTNER Cohort A trial with the Edwards Lifesciences' SAPIEN Transcatheter Heart Valve System (56%) and surgical valves (40%).[49] Thus, the observed rate of device success with the Lotus Valve System (based on the VARC 2 definition) is consistent with what is expected from other transcatheter and surgical valves. Core lab assessment of paravalvular aortic regurgitation at 30 days indicated no severe regurgitation and 1 case of moderate regurgitation; in 79.2% (42/53) of subjects there was trace/trivial or no paravalvular regurgitation. At 30 days, mean EOA was 1.67±0.38 cm^2.

Table 4-4: REPRISE II Secondary Endpoints, ITT Analysis Set (N=60)

Variable	REPRISE II
Device Performance	
Successful vascular access, delivery and deployment of the Lotus Valve System and successful retrieval of the delivery system	100.0% (60/60)
Successful repositioning (partial or complete resheathing of the Lotus Valve in the catheter and redeployment in a more accurate position within the aortic valve annulus) of the Lotus Valve System if repositioning is attempted	100.0% (16/16)
Successful retrieval (complete resheathing of the Lotus Valve in the catheter and removal from the body) of the Lotus Valve System if retrieval is attempted	100.0% (4/4)
Device Success (VARC 2 Definition)[45]	54.5% (24/44)
Absence of procedural mortality	98.3% (59/60)
Correct positioning of a single transcatheter valve in the proper anatomical location	100.0% (60/60)
Intended performance of the Lotus Valve (Discharge) [a]	55.8% (24/43)
Indexed effective orifice area >0.85 cm^2/m^2 [>0.7 cm^2/m^2 for BMI ≥30 kg/m^2]	60.5% (26/43)
Mean aortic valve gradient <20 mmHg	94.6% (53/56)
Peak velocity <3m/sec	94.6% (53/56)
Without moderate or severe prosthetic valve aortic regurgitation	96.4% (54/56)
Aortic Regurgitation (30 Days) [a]	
Central/commissural regurgitation	
None	75.5% (40/53)
Trace/Trivial	17.0% (9/53)
Mild	7.5% (4/53)
Moderate	0.0% (0/53)
Severe	0.0% (0/53)
Paravalvular regurgitation	
None	71.7% (38/53)
Trace/Trivial	7.5% (4/53)
Mild	18.9% (10/53)
Moderate	1.9% (1/53)
Severe	0.0% (0/53)
Combined central/commissural and paravalvular regurgitation	
None	54.7% (29/53)

Table 4-4: REPRISE II Secondary Endpoints, ITT Analysis Set (N=60)

Variable	REPRISE II
Trace/Trivial	24.5% (13/53)
Mild	18.9% (10/53)
Moderate	1.9% (1/53)
Severe	0.0% (0/53)
Effective orifice area at 30 days (cm^2)[a]	1.67±0.38 (39) (0.76, 2.85)

Numbers are % (count/sample size) or mean±SD (n) (minimum, maximum).
Note: "Discharge" represents discharge from hospitalization or 7 days post-procedure, whichever came first.
a: Core lab determination
Abbreviation: ITT=intent-to-treat; N/A=not applicable; VARC=Valve Academic Research Consortium;

4.2.3. Conclusion

Overall, the results from this study have demonstrated acceptable performance and safety of the Lotus Valve System.

5. Device Description

5.1. *Lotus Valve System*

The Lotus Valve System (Figure 5.1-1) has two main parts: a bioprosthetic aortic valve implant and a catheter-based delivery system for introduction and delivery of the valve implant. The device is introduced percutaneously using conventional catheterization techniques. More detailed product information is contained in the Investigator Brochure and Directions for Use (DFU).

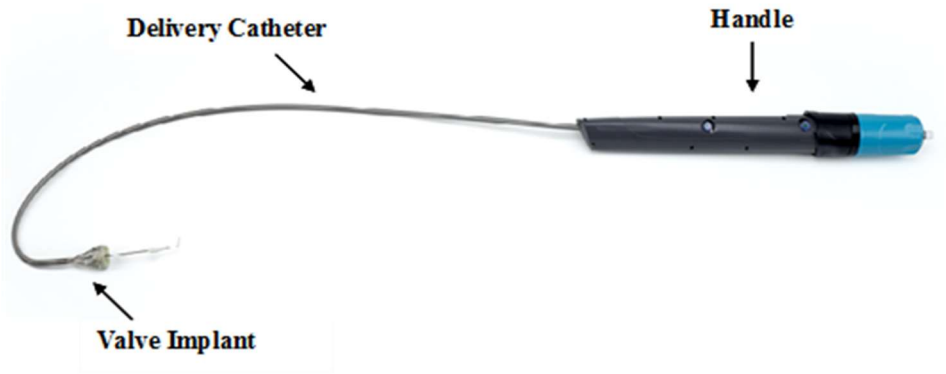

Figure 5.1-1: Lotus™ Valve System

5.1.1. Lotus Valve

The Lotus Valve (Figure 5.1-2) consists of 3 bovine pericardial leaflets. The commissures of the leaflets are attached to the valve frame through portions of the locking components.

The valve frame is made of a single nitinol wire strand woven into a braid. The wire ends of this frame are encapsulated by a tantalum crimp that is used as a radiopaque marker, and which is located in the center of the frame height. The braided structure is designed to foreshorten and expand radially when delivered, and is then locked in this position using a post and buckle locking mechanism.

The Adaptive™ Seal is made of a polycarbonate-based urethane and is located on the outside bottom half of the frame. This seal provides a barrier between the native annulus and the frame to help reduce paravalvular leakage.

The valve is deployed in a beating heart and rapid pacing is not required during valve deployment. The valve begins to function early in the deployment process, providing stabilized hemodynamic functionality.

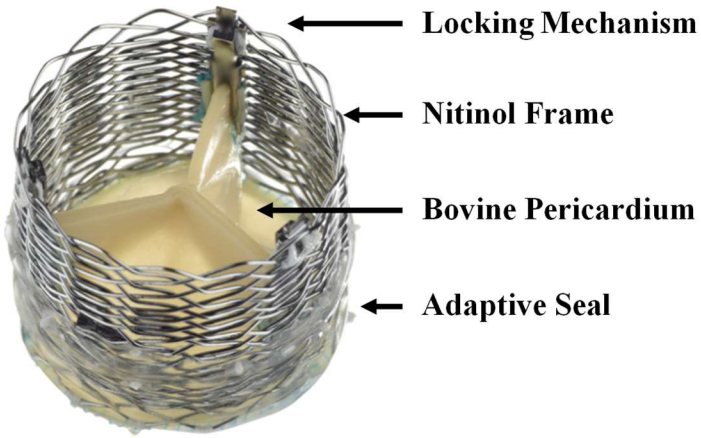

Figure 5.1-2: Lotus Valve Implant

The device is designed so that the radial strength of the frame produces a specified final "as-deployed" diameter when the valve is locked, regardless of the target annulus. The frame height in the deployed state is approximately 19 mm.

5.1.2. Lotus Delivery System

The Lotus Delivery System is made of the catheter and the handle.

- The catheter is a sheath in which mandrels allowing the shortening, locking, unlocking, and elongation of the valve, as well as its releasing, connect from the handle to the valve. The catheter has a hydrophilic coating to facilitate the insertion. The tip of the catheter seats on the shoulder of a nosecone to provide a smooth transition.
- The handle is shown in Figure 5.1-3.
  - The handle has 3 ports; 2 of the ports are for flushing purposes and one is the Guidewire Port.

- The Control Knob at the proximal end of the handle is the primary control used to deploy the valve. It operates both the sheathing/unsheathing function as well as the locking/unlocking function.
  - The sheathing/unsheathing capability allows the implant to be pulled into or pushed out of the outer catheter.
  - The locking function shortens the valve implant into the locked configuration; the unlocking function elongates the valve.
- The Release Collar is used when the operator is ready to release the valve. A sliding door covers the collar to avoid inadvertent premature release.

Figure 5.1-3: Lotus Valve Delivery System – Handle

5.2. *Intended Use*

The Lotus Valve System is intended to improve aortic valve function for symptomatic subjects with severe calcific aortic stenosis (aortic valve area [AVA] of <1.0 cm^2 or AVA index of <0.6 cm^2/m^2) who are at high risk for standard surgical valve replacement.

5.3. *Device Labeling*

A basic description of the device and a comprehensive set of Directions for Use (DFU) are contained in each product package.

6. Objectives

The primary objective of the RESPOND study is to collect real world clinical and device performance outcomes data with the Lotus Valve System used in routine clinical practice to demonstrate that the commercially available Lotus Valve System is a safe and effective treatment for patients with severe calcific aortic stenosis.

7. Endpoints

7.1. *Primary Endpoints*

The primary endpoint for the main cohort of approximately 1000 subjects is all-cause mortality at 30 days and 1 year after the implant procedure. The primary endpoint will be evaluated on an intention-to-treat (ITT) basis (all subjects enrolled, whether or not a Lotus Valve is implanted). All-cause mortality at 30 days after the implant procedure will be compared to a pre-specified performance goal.

The primary endpoint for the additional cohort of approximately 80 subjects is all-cause mortality at 30 days after the implant procedure.

7.2. *Secondary Endpoints*

The following secondary endpoints will be measured according to current VARC guidelines:

- Safety composite of all-cause mortality and disabling stroke at 30 days and 1 year
- In-hospital mortality
- The VARC efficacy composite at 1 year, including all-cause mortality; all stroke (disabling and non-disabling); re-hospitalization for valve-related symptoms or worsening congestive heart failure (NYHA class III or IV); and prosthetic valve-related dysfunction (mean aortic valve gradient ≥20 mmHg, effective orifice area (EOA) ≤0.9–1.1 cm^2 and/or Doppler velocity index (DVI) <0.35 m/s, AND/OR moderate or severe prosthetic valve aortic regurgitation)
- Time related valve safety composite at 1 year, including structural valve deterioration (valve-related dysfunction requiring repeat procedure [TAVI or SAVR]); prosthetic valve endocarditis; prosthetic valve thrombosis; thromboembolic events (e.g. stroke) and VARC bleeding, unless clearly unrelated to valve therapy based on investigator assessment (e.g. trauma)
- Clinical endpoints at 30 days defined according to current VARC guidelines:
  - Life-threatening bleeding
  - Acute kidney injury—Stage 2 or 3 (including renal replacement therapy)
  - Coronary artery obstruction requiring intervention
  - Major vascular complication
  - Valve-related dysfunction requiring repeat procedure (BAV, TAVI, or SAVR)
  - New conduction disturbances (LBBB, AVB, RBBB) and need for permanent pacemaker implantation

- Grade of paravalvular aortic valve regurgitation pre-discharge as measured by transthoracic echocardiography (TTE) and assessed by an independent core laboratory. The moderate and severe paravalvular aortic regurgitation rate will be compared to a pre-specified performance goal.

NOTE: Secondary endpoints will be assessed in the additional cohort of 80 patients through 30 day follow up.

7.3. *Additional Measurements*

Additional measurements will be collected as specified below:

- The following events will be collected based on the current VARC definitions[44,45]:
  - All-cause death (cardiovascular and non-cardiovascular)
  - Stroke: disabling and non-disabling
  - Myocardial infarction (MI): periprocedural (≤72 hours post index procedure) and spontaneous (>72 hours post index procedure)
  - Bleeding: life-threatening (or disabling), major and minor
  - Acute kidney injury (≤7 days post index procedure): based on the AKIN System Stage 3 (including renal replacement therapy), Stage 2, and Stage 1
  - Major and minor vascular complication
  - Repeat procedure for valve-related dysfunction (surgical or interventional therapy)
  - Hospitalization for valve-related symptoms or worsening congestive heart failure (NYHA class III or IV)
  - New permanent pacemaker implantation resulting from new or worsened conduction disturbances (including new left bundle branch block [LBBB] and third degree atrioventricular block)
  - New onset of atrial fibrillation or atrial flutter
  - Coronary obstruction (periprocedural)
  - Ventricular septal perforation (periprocedural)
  - Mitral apparatus damage (periprocedural)
  - Cardiac tamponade (periprocedural)
  - Prosthetic aortic valve malapposition, including valve migration, valve embolization, ectopic valve deployment, or transcatheter aortic valve (TAV)-in-TAV deployment
  - Prosthetic aortic valve thrombosis
  - Prosthetic aortic valve endocarditis
- Device performance measured peri- and post-procedurally consisting of the following:
  - Successful vascular access, delivery and deployment of the Lotus Valve System, and successful retrieval of the delivery system
  - Successful repositioning (partial or complete resheathing of the Lotus Valve in the catheter and redeployment in a more accurate position within the aortic valve annulus) of the Lotus Valve System if repositioning is attempted

  - Successful retrieval (complete resheathing of the Lotus Valve in the catheter and removal from the body) of the Lotus Valve System if retrieval is attempted
  - Grade of paravalvular aortic valve regurgitation
- Physicians Preference Test (PPT), including device deficiencies, to measure device usability and ease of use peri-procedurally.
- Prosthetic aortic valve performance as measured by transthoracic echocardiography (TTE) and assessed by an independent core laboratory, including effective orifice area, mean and peak aortic gradients, peak aortic velocity, and grade of aortic regurgitation pre-discharge and at 1 year. Site reported TTE measures will be collected at 30 days and annually from 2 through 5 year follow up per local standard of care for TAVI.
- Health status as evaluated by EuroQoL (EQ-5D) Quality of Life questionnaire at baseline, 30 days, 1, 3 and 5 year follow up, during in-person clinic visit or via postal mail.
- New York Heart Association (NYHA) functional classification at baseline, procedure, discharge, 30 days, 1 year and annually through 5 year follow up.

NOTE: Secondary endpoints will be assessed in the additional cohort of 80 patients through 30 day follow up.

8. Study Design

The RESPOND study is a prospective, open label, single arm, multi-center, observational post market study designed to collect real world clinical and device performance outcomes data of the commercially available Lotus Valve used in routine clinical practice for the treatment of severe calcific aortic stenosis. The main cohort of approximately 1000 real-world, prospective, consecutive subjects will be enrolled at up to 60 study centers in Europe, Asia Pacific and South America. An additional cohort of approximately 80 subjects will be enrolled after enrollment is complete in the main cohort at up to 8 centers in Europe.

NOTE: Consecutive is defined as a commitment by the participating investigators at each study center to enroll all consented patients admitted for Transcatheter Aortic Valve Implantation (TAVI) who are selected to receive a Lotus Valve.

All implanted subjects enrolled in the main cohort will be contacted for follow-up at 30 days, 1, 2, 3, 4 and 5 years post index valve implantation. Follow-up visit at 1 year post valve implantation should be conducted via outpatient clinic visit. Follow-up visits at 30 days and 2 through 5 years may be conducted in person (preferred) and via telephone interview. Subjects who are not implanted with a Lotus Valve will be followed for safety through 30 days after the initial attempted index procedure.

The approximately 80 subjects enrolled in the additional cohort will be contacted for follow up at 30 days post valve implantation, at which point their participation in the study will be complete.

Collection of safety events will include any serious adverse event (SAE) that led to death, adverse device effect (ADE), serious adverse device effect (SADE), unanticipated serious

adverse device effect (USADE), and all VARC events regardless of seriousness and device relationship through 5 year follow-up for the main cohort and through 30 days for the additional 80-subject cohort.

The RESPOND study will be conducted in accordance with the International Standard ISO 14155: 2011; ethical principles that have their origins in the Declaration of Helsinki; the relevant parts of the International Conference on Harmonization (ICH) Guidelines for Good Clinical Practices (GCP); and pertinent individual country/state/local laws and regulations.

8.1. *Justification for the Study Design*

In order to support the stated objectives of this study (see Section 6), approximately 1000 subjects will be enrolled in the study at up to 60 study centers in Europe, Asia Pacific and South America. Planned interim analyses of the primary and secondary endpoints will be performed on the first 250 and 500 enrolled subjects. A final analysis of the primary and secondary endpoints will be conducted on the main study cohort (N=1000). All implanted subjects will be followed for 5 years post index procedure.

After enrollment in the main cohort is completed an additional cohort of approximately 80 subjects will be enrolled in the study at up to 8 centers in Europe to assess center-driven implantation technique with the commercially available Lotus Valve System. Due to acute assessment of the implant technique, subjects enrolled in the additional cohort will be contacted for follow up at 30 days post valve implantation, at which point their participation in the study will be complete.

9. Subject Selection

All patients who are candidates for TAVI, signed the informed consent form and are selected to receive a Lotus Valve will be evaluated for enrollment in this study.

10. Subject Accountability

10.1. *Point of Enrollment*

A subject is considered enrolled upon obtaining a signed Informed Consent Form (ICF) from the subject or subject's legally authorized representative (LAR) and an attempt to insert the Lotus Introducer sheath.

11. Study Methods

11.1. *Data Collection*

Table 11.1-1 below lists the schedule of observations and assessments planned during this study. Data collection at baseline, index procedure, discharge and each follow-up should be based on the study center's standard of care for TAVI.

Table 11.1-1: Study Event Schedule

Procedure/Assessment	Baseline	Index Procedure	Post-procedure/ Pre-discharge	Follow-up Visits	
				30 Days[1] (± 7 Days) Office Visit or Telephone Interview	1-5 Years[1, 10] (± 45 Days) Annual Office Visit or Telephone Interview
Demographics, physical assessment, risk factors and medical history	X				
NYHA Classification	X		X	X	X
Risk assessment[2]	X				
Frailty assessment[3]	X				
CT angiogram of aortic structure and iliofemoral system[4]	X				
Procedural cine-angiogram[5]		X			
Heart rhythm[6]	X	X	X	X	X
Physician Preference Test		X			
Antiplatelet and other cardiovascular medications	X	X	X	X	X
Transthoracic echocardiography (TTE)[7]	X		X	X	X
QOL questionnaire[8]	X			X	X
SAE that led to death, ADE/SADE, USADE, device deficiency assessment and all VARC events[9]		X	X	X	X

[1] All follow-up dates will be calculated from the date of the index procedure. Follow-up visits may be conducted in person (preferred) and via telephone. Subjects with implant failures will be followed for safety through 30 days after the initial attempted index procedure.

[2] Consists of EuroSCORE 2011 or STS score.

[3] Frailty assessment at baseline, including nutritional assessment (body mass index), strength and balance (gait speed, maximal grip strength) and activities of daily living (Katz index) should be captured if performed according to local standard of care.

[4] Computed tomography (CT) angiogram of the aortic structure (from aortic annulus to the aortic distal bifurcation) and the iliofemoral bifurcation should be performed prior to the index procedure to evaluate the aortic valve anatomy, aortic root dimensions for device sizing and access assessment. CT angiogram should be performed according to the standard of care for TAVI. For the additional cohort of up to 80 subjects, baseline CT angiograms must be sent to the CT Core Laboratory for independent analysis.

[5] The procedural cine-angiogram should be submitted to Boston Scientific.

[6] Underlying heart rhythm, including data from the most recent pacemaker interrogation done by an electrophysiologist or in a device clinic per local standard of care for subjects who received a permanent pacemaker related to the index procedure. Pacemaker interrogation should also include assessment of pacer dependence.

[7] TTE should be performed at baseline, discharge, 30 days, 1 year and annually through 5 year follow up or per local standard of care for TAVI, if TTE frequency or requirements are different from study schedule. TTE performed at baseline, pre-discharge and 1 year after Lotus Valve implant must be sent to the Echocardiography Core Laboratory for independent analysis.

[8] The EQ-5D QOL questionnaire at baseline should be performed within 30 days of the index procedure. Additional

Table 11.1-1: Study Event Schedule

Procedure/Assessment	Baseline	Index Procedure	Post-procedure/ Pre-discharge	Follow-up Visits	
				30 Days[1] (± 7 Days) Office Visit or Telephone Interview	1-5 Years[1, 10] (± 45 Days) Annual Office Visit or Telephone Interview

surveys should be performed at 30 days, 1, 3 and 5 years post index procedure during office visits or via mail.

[9] Safety events will be monitored and reported to BSC from the time of enrollment through 5 year follow-up for the main cohort and through 30-day follow-up for the additional 80-subject cohort. For subjects who do not receive a Lotus Valve, events will be collected and reported through 30 days after the initial attempted index procedure.

[10] The additional cohort of up to 80 subjects will be followed through 30 days post implant procedure; 1-5 year follow up does not apply.

Abbreviations: ADE=adverse device effect; CT=computerized tomography; ECG=electrocardiogram; NYHA=New York Heart Association; QOL=Quality of Life; SADE=serious adverse device effect; SAE=serious adverse event; TAVI=transcatheter aortic valve implantation; TTE=transthoracic echocardiography; USADE=unanticipated serious adverse device effect.

11.2. *Study Candidate Screening*

Subjects will be evaluated for eligibility by the clinical site's heart team per the local standard of practice. The heart team is generally comprised of interventional cardiologist, cardiac surgeon, cardiologist, echocardiographer, imaging specialist, anesthesiologist, nurse practitioner, etc. Assessment will be based on results from the Society of Thoracic Surgeons (STS) score (≥8%) and/or agreement by the heart team (including a cardiac surgeon's documented evaluation) that the subject is at high operative risk of serious morbidity or mortality with surgical valve replacement. The heart team (including an experienced cardiac surgeon's assessment) must also agree that the subject is likely to benefit from valve replacement.

11.3. *Informed Consent*

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

11.4. *Baseline*

The following assessments should be completed prior to the index procedure, per local standard of care for TAVI. The study eCRFs identify the specific data points to be collected.

- Confirmation of eligibility and contraindications per the DFU
- Demographics, physical assessment, risk factors and medical history
- New York Heart Association (NYHA) classification
- Risk assessment, including EuroSCORE 2011 or STS score
- The following frailty assessment
    - Nutritional assessment (body mass index)

  - Strength and balance (gait speed, maximal grip strength, walking aid dependency)
  - Activities of daily living (Katz Index)
- Angio CT scan of the aortic structure (from aortic annulus to the aortic distal bifurcation) and the iliofemoral bifurcation should be performed prior to the index procedure to evaluate the aortic valve anatomy, aortic root dimensions for device sizing and access assessment. For the additional cohort of up to 80 subjects , baseline CT angiograms must be sent to the CT Core Laboratory for independent analysis.
- Underlying heart rhythm
- Antiplatelet or other cardiovascular medications
- Transthoracic Echocardiography (TTE), including assessment of effective orifice area, peak systolic and mean aortic valve gradient pressure, aortic regurgitation assessment, mitral regurgitation, LVEF, left ventricular end-diastolic and end-systolic diameter, TR jet velocity and LA volume. A baseline TTE for subjects implanted with a Lotus Valve must be sent to the Echocardiography Core Laboratory for independent analysis.
- EQ-5D Quality of Life Questionnaire

11.5. *Index Procedure*

The preparation of the subject for the percutaneous procedure will be performed following standard techniques. Refer to the Lotus Valve System DFU for detailed instructions about preparation and placement of the Lotus Valve.

It is recommended that a stiff guidewire (e.g., Safari) is used during the Lotus Valve implant procedure.

11.6. *Post-procedure / Prior to Hospital Discharge*

The subject may be discharged from the hospital when clinically stable, at the Investigator's discretion per local standard of care. Prior to discharge from the hospital, the following data is to be collected:

- Complete safety event assessment, including any SAE that led to death, ADE, SADE, USADE, device deficiency with associated treatment, and any VARC event regardless of seriousness and device relationship.
- Per the expert consensus document on TAVI, antiplatelet therapy with aspirin and a thienopyridine is recommended to decrease the risk of thrombotic or thromboembolic complications if there are no contraindications to these medications[43]. Subjects should be treated with aspirin and clopidogrel for at least 1 month following valve implantation. Subsequent antiplatelet therapy should be at the investigator's discretion, or in accordance with country-specific labeling for the medications. If oral anti-coagulation is indicated after valve implantation, antiplatelet therapy should consist of either aspirin or thienopyridine. Combination treatment with oral anti-coagulation and dual antiplatelet therapy after valve implantation should be avoided.
- Underlying heart rhythm
- NYHA classification

- TTE, including assessment of effective orifice area, peak systolic and mean aortic valve gradient pressure, aortic regurgitation assessment, mitral regurgitation, LVEF, left ventricular end-diastolic and end-systolic diameter, TR jet velocity and LA volume, per local standard of care. A pre-discharge TTE for subjects implanted with a Lotus Valve must be sent to the Echocardiography Core Laboratory for independent analysis.

Prior to discharge, clinical staff should review the study follow-up visit schedule with the subject to maximize follow-up compliance.

11.7. *Follow-up*

All implanted subjects enrolled in the main cohort of 1000 subjects will be evaluated at 30 days, 1, 2, 3, 4 and 5 years post index procedure. Follow-up visit at 1 year post valve implantation should be conducted via outpatient clinic visit. Follow-up visits at 30 days and 2 through 5 years may be conducted in person (preferred) and via telephone interview. Subjects with no Lotus Valve implanted will be followed for safety through 30 days after the initial attempted index procedure.

The additional cohort of approximately 80 subjects will be contacted for follow up at 30 days post valve implantation.

It is important that the follow-up visit schedule be maintained as closely as possible for all subjects. Boston Scientific recognizes that subjects may not be able to return for all scheduled visits at precisely the date required, and therefore, a period of time in which each visit should be conducted is indicated in Table 11.1-1. Each follow-up visit must be performed by trained study personnel. Data from collected tests and images as well as medical assessments will be recorded in source documentation and captured in the eCRFs.

In the event that study personnel learn of a subject's hospitalization outside the study center, the center should make every effort to obtain copies of reports or results based on tests (e.g., echocardiogram) and/or procedures performed on the study subject.

11.7.1. 30-Day Follow-up (30±7 days)

All enrolled subjects must be evaluated 30 days after the index procedure. The 30-day follow-up visit may be conducted in person (preferred) or via telephone interview. During the 30-day follow-up, the following assessments are to be collected:

- Complete safety event assessment, including any SAE that led to death, ADE, SADE, USADE, device deficiencies with associated treatment, and any VARC events regardless of seriousness and device relationship.
- All antiplatelet and other cardiovascular medications administered in accordance with society guidelines[43] and local standard of care. Subjects should be treated with aspirin and clopidogrel for at least 1 month following valve implantation. Subsequent antiplatelet therapy should be at the investigator's discretion, or in accordance with country-specific labeling for the medications. If oral anti-coagulation is indicated after valve implantation, antiplatelet therapy should consist of either aspirin or thienopyridine. Combination

treatment with oral anti-coagulation and dual antiplatelet therapy after valve implantation should be avoided.
- Underlying heart rhythm, including assessment of pacemaker dependency for subjects who had a pacemaker implanted after the index procedure.
- NYHA classification
- TTE, including assessment of effective orifice area, peak systolic and mean aortic valve gradient pressure, aortic regurgitation assessment, mitral regurgitation, LVEF, left ventricular end-diastolic and end-systolic diameter, TR jet velocity and LA volume, per local standard of care.
- EQ-5D Quality of Life Questionnaire during office visit or via mail.

11.7.2. Annual Follow-up (±45 days)

All implanted subjects enrolled in the main cohort of 1000 subjects will be evaluated at 1, 2, 3, 4 and 5 years after the index procedure. Follow-up visit at 1 year post valve implantation should be conducted via outpatient clinic visit. Annual follow-up visits at 2 through 5 years may be conducted in person (preferred) or via telephone interview. During annual follow-up, the following assessments are to be collected:

- Complete safety event assessment, including any SAE that led to death, ADE, SADE, USADE, device deficiencies with associated treatment, and any VARC events regardless of seriousness and device relationship.
- All antiplatelet and other cardiovascular medications administered in accordance with society guidelines[43] and local standard of care.
- Underlying heart rhythm, including assessment of pacemaker dependency for subjects who had a pacemaker implanted after the index procedure.
- NYHA classification
- TTE, including assessment of effective orifice area, peak systolic and mean aortic valve gradient pressure, aortic regurgitation assessment, mitral regurgitation, LVEF, left ventricular end-diastolic and end-systolic diameter, TR jet velocity and LA volume, per local standard of care. A TTE performed 1 year after valve implantation must be sent to the Echocardiography Core Laboratory for independent analysis.
- EQ-5D Quality of Life Questionnaire during office visit or via mail at 1 year, 3 year and 5 year follow-up.

11.8. *Withdrawal and Replacement of Subjects*

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 reason for withdrawal will be recorded (if given) in all cases of withdrawal. 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 used for analysis but no new data will be collected after withdrawal.

11.9. *Study Completion*

All implanted subjects enrolled in the main cohort of 1000 subjects will be followed for the duration of 5 years post index procedure. A subject's participation in the study will conclude after completion of the 5 year follow-up visit.

For subjects enrolled in the additional 80-subject cohort, participation in the study will conclude after completion of the 30-day follow-up visit.

12. Statistical Considerations

12.1. *Endpoints*

12.1.1. Primary Endpoint (Main Cohort)

The study is powered to assess one primary endpoint, which is all-cause mortality at 30 days post implant as assessed by an independent CEC. The null and alternative hypotheses for the primary device performance endpoint are as follows.

H_0: $Mortality_{30D} \geq PG$

H_1: $Mortality_{30D} < PG$

where $Mortality_{30D}$ is the 30-day all-cause mortality rate for the Lotus Valve and PG is 14%.

A one-sample exact binominal test will be used to test the one-sided hypothesis. The all-cause mortality at 1 year post implant will be summarized using descriptive statistics.

12.1.1.1. Hypothesis (Main Cohort)

All-cause mortality at 30 days post implant procedure is less than the PG of 14 % (expected rate of 10% + testing margin of 4%)

12.1.1.2. Sample Size – Primary Endpoint (Main Cohort)

The sample size calculation for the primary endpoint is based on the following assumptions:

- Expected 30-day all-cause mortality rate = 10%
- Performance goal (PG) = 14% (expected rate of 10% + testing margin of 4%)
- Test significance level (α) = 0.025 (1-sided)
- Power ($1 - \beta$) > 95%
- Planned enrollment of up to 1000 subjects
- Two planned interim analyses on the primary endpoint at 30 days post-implant procedure will be performed on the first 250 and 500 subjects enrolled. A final analysis will be performed on all enrolled subjects
- The primary analysis population for the primary endpoint will be the subject population attempted or implanted with the Lotus Valve.

Note: The expected 30-day all-cause mortality rate is assumed to be 10% based on a literature review of studies evaluating the Medtronic CoreValve System and the Edwards Lifesciences SAPIEN Transcatheter Heart Valve System (FRANCE 2 registry[36]).

***Note*:** The alpha-level for the interim and final analyses is adjusted using the Pocock alpha spending function[50] (see Section 12.3.2).

12.1.2. Secondary Endpoint (Main Cohort)

The study is powered to assess one secondary endpoint, which is grade of paravalvular aortic valve regurgitation pre-discharge as assessed by TTE post valve implantation. The null and alternative hypotheses for the primary device performance endpoint are as follows.

H_0: $AR_{pre\text{-}discharge} \geq PG$

H_1: $AR_{pre\text{-}discharge} < PG$

where $AR_{pre\text{-}discharge}$ is the proportion of subjects with moderate/severe aortic regurgitation pre-dischage post implant procedure for the Lotus Valve and PG is 16.5%.

A one-sample exact binominal test will be used to test the one-sided hypothesis.

12.1.2.1. Hypothesis (Main Cohort)

Proportion of subjects with moderate/severe aortic regurgitation pre-discharge as assessed by TTE post implant procedure is less than the PG of 16.5%.

12.1.2.2. Sample Size – Secondary Endpoint (Main Cohort)

The sample size calculation for the secondary endpoint is based on the following assumptions:

- Expected proportion of subjects with moderate/severe aortic regurgitation pre-discharge as assessed by TTE post valve implantation = 10%
- Performance goal (PG) = 16.5% (based on FRANCE 2 registry[36])
- Test significance level (α) = 0.025 (1-sided)
- Power ($1 - \beta$) > 99%
- Planned enrollment of up to 1000 subjects
- Two planned interim analyses on the secondary endpoint prior to discharge from the hospital post-implant procedure will be performed on the first 250 and 500 subjects enrolled. A final analysis will be performed on all enrolled subjects.
- The primary analysis population for the secondary endpoint will be the subject population implanted with the Lotus Valve.

Note: The performance goal is set at 16.5% based on rates observed with Medtronic CoreValve System and the Edwards Lifesciences SAPIEN Transcatheter Heart Valve System (FRANCE 2 registry).

***Note*:** The alpha-level for the interim and final analyses is adjusted using the Pocock alpha spending function (see Section 12.3.2).

12.1.3. Statistical Methods

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. The distribution of prognostic factors between subjects with and without data will be examined. Methods to eliminate or minimize bias will be implemented and described completely. Statistical models that account for censored data will be employed in appropriate circumstances (e.g., for time-to-event outcomes). Sensitivity analyses, including a tipping-point analysis for the primary endpoint, will be conducted to assess the impact of different assumptions on interpretation of the results. Outlier values will be evaluated for their validity. Suspected invalid data will be queried and corrected in the database prior to statistical analysis.

The data of the additional cohort of approximately 80 subjects will be summarized using descriptive statistics and will not be pooled with the first cohort of 1,000 subjects in the data analysis. No statistical hypotheses will be tested in the additional cohort.

12.2. *General Statistical Methods*

12.2.1. Analysis Sets

The primary endpoint will be evaluated on an ITT basis (all subjects enrolled, whether or not a study device is implanted). For the ITT analysis, all subjects who sign the written ICF and are enrolled in the study will be included in the analysis sample, regardless of whether the study device was implanted.

The primary analysis population for the secondary endpoint will be the subject population implanted with the Lotus Valve (as-treated subject population).

12.2.2. Control of Systematic Error/Bias

The selection of patients will be made from the Investigator's usual case load. All subjects who have signed the ICF and are selected to receive a Lotus Valve will be enrolled 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.

12.3. *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).

12.3.1. Risk Adjusted Analysis

Risk adjusted clinical outcomes by valve size will be analyzed on the subject population implanted with the Lotus Valve (as-treated subject population).

12.3.2. Interim Analyses

Two interim analyses for the primary and secondary endpoints will be conducted on the first 250 and 500 subjects, and a final analysis will be conducted on the planned 1000 subjects of the main cohort. The Pocock alpha spending function[50] is used to adjust the alpha-level for each analysis: 0.00894, 0.00895, and 0.01301, respectively. If the *P* value from the one-sample exact binominal test is <alpha, the Lotus Valve will be concluded to have event rate < PG. This corresponds to the one-sided Clopper-Pearson upper (1-alpha)% confidence bound of the observed event rate being < PG.

The two planned interim analyses are pre-specified to provide a formal hypothesis testing approach to examine the primary and secondary endpoints with the adjusted significance level. There is no plan to stop the subject enrollment even if the null hypothesis is rejected at each of the two planned interim analyses.

12.3.3. Changes to Planned Analyses

Any changes to the planned statistical analyses will be documented in an amended Statistical Analysis Plan.

13. Data Management

13.1. *Data Collection, Processing, and Review*

Subject data will be recorded in a limited access secure electronic data capture (EDC) system.

The clinical database will reside on a production server hosted by Medidata. All changes made to the clinical data will be captured in an electronic audit trail and available for review by Boston Scientific Corporation (BSC) or its representative. The associated RAVE software and database have been designed to meet regulatory compliance for deployment as part of a validated system compliant with laws and regulations applicable to the conduct of clinical studies pertaining to the use of electronic records and signatures. Database backups are performed regularly.

The Investigator provides his/her electronic signature on the appropriate electronic case report forms (eCRFs) in compliance with local regulations. A written signature on printouts of the eCRFs must also be provided if required by local regulation. Changes to data previously submitted to the sponsor require a new electronic signature by the Investigator acknowledging and approving the changes.

Visual and/or electronic data review will be performed to identify possible data discrepancies. Manual and/or automatic queries will be created in the EDC system and will be issued to the site for appropriate response. Site staff will be responsible for resolving all queries in the database.

13.2. *Record Retention*

The Investigator will maintain, at the study center, in original format all essential study documents and source documentation that support the data collected on the study subjects in compliance with ICH/GCP guidelines. Documents must be retained for at least 2 years after the last approval of a marketing application or until at least 2 years have elapsed since the formal discontinuation of the clinical investigation of the product. These documents will be retained for a longer period of time by agreement with BSC or in compliance with other local regulations. It is BSC's responsibility to inform the Investigator when these documents no longer need to be maintained. The Investigator will take measures to ensure that these essential documents are not accidentally damaged or destroyed. If for any reason the Investigator withdraws responsibility for maintaining these essential documents, custody must be transferred to an individual who will assume responsibility and BSC must receive written notification of this custodial change.

13.3. *Core Laboratory*

An independent Core Laboratory will review baseline, pre-discharge and 1 year follow up echocardiography images from all centers and every enrolled subject implanted with a Lotus Valve for qualitative and quantitative analysis. These analyses will minimize bias and inconsistencies by providing an independent interpretation of all measurements using standard techniques.

An independent Core Laboratory will review baseline CT angiograms for the additional cohort of approximately 80 subjects that are implanted with a Lotus Valve to evaluate the aortic valve anatomy and aortic root dimensions for device sizing. These analyses will minimize bias and inconsistencies by providing an independent interpretation of all measurements using standard techniques.

14. Amendments

If a protocol revision is necessary which affects the rights, safety or welfare of the subject or scientific integrity of the data, an amendment is required. Appropriate approvals (e.g., IRB/EC) of the revised protocol must be obtained prior to implementation.

15. Deviations

All deviations from the protocol, with the reason for the deviation and the date of occurrence, must be documented and reported to the sponsor using the EDC CRF. Study centers may also be required to report deviations to the IRB/EC, per local guidelines and government regulations.

16. Compliance

16.1. *Statement of Compliance*

The RESPOND study will be conducted in accordance with the International Standard ISO 14155: 2011, ethical principles that have their origins in the Declaration of Helsinki, the relevant parts of the International Conference on Harmonization (ICH) Guidelines for Good Clinical Practices (GCP), and pertinent individual country laws and regulations.

16.2. *Investigator Responsibilities*

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

16.3. *Institutional Review Board/ Ethics Committee*

Prior to gaining Approval-to-Enroll status, the investigational center will provide to the sponsor documentation verifying that their IRB/EC is registered or that registration has been submitted to the appropriate agency, as applicable according to national/regulatory requirements.

A copy of the written IRB/EC approval of the protocol (or permission to conduct the study) and ICF, must be received by the sponsor 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.

Annual IRB/EC approval and renewals will be obtained throughout the duration of the study as required by local/country or IRB/EC requirements. Copies of the Investigator's reports and the IRB/EC continuance of approval must be provided to the sponsor.

16.4. *Sponsor Responsibilities*

All information and data sent to BSC concerning subjects or their participation in this study will be considered confidential by BSC. Only authorized BSC personnel or a BSC representative including Contract Research Organization (CRO) will have access to these confidential records. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this study. Study data collected during this study may be used by BSC for the purposes of this study, publication, and to support future research and/or other business purposes. All data used in the analysis and reporting of this study will be without identifiable reference to specific subject name.

Boston Scientific will keep subjects' health information confidential in accordance with all applicable laws and regulations. Boston Scientific may use subjects' health information to conduct this study, as well as for additional purposes, such as overseeing and improving the performance of its device, new medical research and proposals for developing new medical

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

16.5. *Insurance*

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

17. Training

Boston Scientific has established a structured training program for the physicians and staff (Heart Team) who will be involved in the peri-procedural care of the Lotus patients. This training program is designed to provide the physicians and staff with the information and experience necessary to control user-associated risks when the device is used in accordance with the DFU. Training records shall be maintained as evidence that physicians have received appropriate training. This training program includes proctored cases on site.

Operators must complete the required training and proctorship (6-8 proctored cases), and perform a minimum of 2 independent cases using commercial Lotus Valve System prior to being authorized to participate in this study.

18. Monitoring

Monitoring visits to the clinical sites will be made periodically during the study, to ensure that all aspects of the current, approved protocol/amendment(s) are followed.

Original source documents will be reviewed for verification of data in the electronic database for:

- A random sample of 10% of subjects enrolled at each clinical site.
- Subjects with ADE, SADE, USADE, VARC events, or device deficiencies associated with the Lotus Valve System implanted during the index procedure.
- Subjects with CEC events (i.e. death and stroke).
- Informed Consent for all enrolled and screen failure subjects at each clinical site.

The Investigator/institution guarantees direct access to original source documents (including electronic medical records) by BSC personnel, their designees, and appropriate regulatory authorities. In the event that the original medical records cannot be obtained for a patient that is seen by a non-study physician at a non-study institution, photocopies of the original source documents should be made available for review.

The study also may be subject to a quality assurance audit by BSC or its designees, as well as inspection by appropriate regulatory authorities.

19. Potential Risks and Benefits

19.1. *Potential Risks*

Adverse events potentially associated with transcatheter aortic valve implantation as well as additional risks related to the use of the Lotus Valve System are listed in the Directions for Use and Informed Consent Form.

19.2. *Potential Benefits*

Transcatheter aortic valve implantation may offer certain advantages when compared to surgical replacement of the stenotic native aortic valve, particularly in high risk subjects. These include the benefits of a minimally invasive procedure and a reduction in the risks related to open heart surgery.

20. Informed Consent

Subject participation in this clinical study is voluntary. Informed Consent is required from all subjects or their legally authorized representative. The Investigator is responsible for ensuring that Informed Consent is obtained.

The obtaining and documentation of Informed Consent must be in accordance with the principles of the Declaration of Helsinki, ISO 14155, any applicable national regulations, and local Ethics Committee and/or Regulatory authority body, as applicable. The ICF must be approved by the center's IRB/EC.

Boston Scientific will provide a study-specific template of the ICF to investigators participating in this study. The ICF template may be modified to meet the requirements of the investigative center's IRB/EC. Any modification requires approval from BSC prior to use of the form. The ICF must be in a language understandable to the subject and if needed, BSC will assist the center in obtaining a written consent translation. Translated consent forms must also have IRB/EC approval prior to their use. Privacy language shall be included in the body of the form or as a separate form as applicable.

21. Safety Reporting

21.1. *Definitions and Classification*

Adverse event definitions are provided in Table 21.1-1. Administrative edits were made to combine definitions from ISO 14155-2011 and MEDDEV 2.7/3 12/2010.

Table 21.1-1: Adverse Event Definitions

Term	Definition
Adverse Device Effect (ADE)	Adverse event related to the use of an investigational medical device NOTE 1: This definition includes any adverse event resulting from

Table 21.1-1: Adverse Event Definitions

Term	Definition
Ref: ISO 14155-2011 *Ref: MEDDEV 2.7/3 12/2010*	insufficient or inadequate instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device. NOTE 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.
Serious Adverse Event (SAE) *Ref: ISO 14155:2011*	Adverse event that: Led to a death Led to serious deterioration in the health of the subject, that either resulted in: o a life-threatening illness or injury, or o a permanent impairment of a body structure or a body function, or o in-patient or prolonged hospitalization, or o medical or surgical intervention to prevent life- threatening illness or injury or permanent impairment to a body structure or a body function, o Led to foetal distress, foetal death or a congenital abnormality or birth defect **Note**: For the purpose of this study, only events that led to death will be reported as SAE.
Serious Adverse Device Effect (SADE) *Ref: ISO 14155-2011* *Ref: MEDDEV 2.7/3 12/2010*	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated Serious Adverse Device Effect (USADE) *Ref: ISO 14155-2011* *Ref: MEDDEV 2.7/3 12/2010*	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 1**: 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 14155-2011* *Ref: MEDDEV 2.7/3 12/2010*	A device deficiency is any inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. **NOTE 1**: Device deficiencies include malfunctions, misuse or use errors, and inadequate labeling.

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

Death should not be recorded as an event, but should only be reflected as an outcome of a specific SAE (see Table 21.1-1 for AE definitions).

Any reportable safety event (see Section 8) experienced by the study subject from the point of enrollment in the study must be recorded in the eCRF. Collect any SAE that led to death and any VARC event regardless of seriousness and device relationship.

Refer to Section 19 for the known risks associated with the study device(s).

21.2. *Relationship to Study Device(s)*

The Investigator must assess the relationship of the event to the study device as related or unrelated. See criteria in Table 21.2-1.

Table 21.2-1: Criteria for Assessing Relationship of Study Device to Adverse Event

Classification	Description
Unrelated	The adverse event is determined to be due to a concurrent illness or effect of another device/drug and is not related to the investigational product.
Related	• The adverse event is determined to be potentially related to the investigational product, and an alternative etiology is equally or less likely compared to the potential relationship to investigational product, or • There is a strong relationship to investigational product, or recurs on re-challenge, and another etiology is unlikely, or • There is no other reasonable medical explanation for the event.

21.3. *Investigator Reporting Requirements*

Event reporting on RESPOND study is limited to SAE that lead to death, ADE, SADE, USADE, device deficiencies and VARC events regardless of seriousness and device relationship. The communication requirements for reporting to BSC are as shown in Table 21.3-1.

Table 21.3-1: Investigator Reporting Requirements

Event Classification	Communication Method	Communication Timeline
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[1]. • Terminating at the end of the study
Serious Adverse Event (SAE) that led to death, Serious Adverse Device Effects (SADE), and serious VARC events	Complete AE eCRF page with all available new and updated information	• Within 2 business days of first becoming aware of the event[1] or as per local/regional regulations. • Reporting required through the end of the study
	Provide relevant source documentation (unidentified) for reported event	• When documentation is available
Adverse Device Effects and non-serious VARC events	Complete AE eCRF page with all available new and updated information	• As soon as possible after becoming aware of the information[1] • Reporting required through the end of the study
Device Deficiencies (including but not limited to failures,	Complete applicable CRF fields/forms with all available new and updated	• Within 1 business day of first becoming aware of the event[1]

Table 21.3-1: Investigator Reporting Requirements

Event Classification	Communication Method	Communication Timeline
malfunctions, and product nonconformities) Note: Any Device Deficiency that might have led to a serious adverse device effect 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.	information.	and as per local/regional regulations • Reporting required through the end of the study

[1] The "become aware date" for an event that requires reporting per the protocol is the date that study personnel listed on the Delegation of Authority Log identify or are notified of the event. Personnel may become aware via any of the following (inclusive but not limited to):

- Patient or patient's caregiver
- Admission / visit with any study personnel
- Patient's non-study physician, nurse or other medical personnel
- Medical record review
- Electronic medical record notification / alert, if applicable at institution

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

21.4. *Device Deficiencies*

All device deficiencies (including but not limited to failures, malfunctions, use errors, product nonconformities, and labeling errors) 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. If it is not possible to return the device, the investigator should document why the device was not returned and the final disposition of the device. Device failures and malfunctions should also be documented in the subject's medical record.

Device deficiencies (including but not limited to failures, malfunctions, and product nonconformities) are not to be reported as events. However, if there is an event that results from a device failure or malfunction, that specific event would be recorded on the appropriate eCRF as outlined in Table 21.3-1.

And, any Device Deficiency that might have led to a serious adverse device effect 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.

22. Committees

22.1. *Steering Committee*

A Steering Committee will be comprised of the sponsor's clinical management, interventional cardiologists and cardiac surgeons, including the study co-principal

investigators, other investigators, and medical consultants experienced in TAVI. Responsibilities may include oversight of the overall conduct of the study with regard to protocol development, study progress, patient safety, overall data quality and integrity, and 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.

22.2. *Clinical Events Committee*

An independent medical reviewer (IMR) will review and adjudicate all-cause mortality and stroke events reported by study investigators. The IMR will review a safety event dossier, which may include copies of subject source documents provided by study sites, and adjudicate study endpoint related clinical events. The responsibilities, qualifications, membership, and procedures of the medical reviewer are outlined in the CEC charter.

23. Suspension or Termination

23.1. *Criteria for Terminating the Study*

Boston Scientific reserves the right to terminate the study but intends to exercise this right only for valid scientific or administrative reasons and reasons related to protection of subjects. Investigators and associated IRBs/ECs will be notified in writing in the event of termination.

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

Boston Scientific reserves the right to suspend/terminate a study center at any time after the study initiation visit if no subjects have been enrolled or if the center has multiple and/or major protocol violations without justification or fails to follow remedial actions.

24. Publication Policy

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

- All authorship and contributorship requirements as described above must be followed.

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

25. Bibliography

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26. Abbreviations and Definitions

26.1. *Abbreviations*

Abbreviations are shown in Table 26.1-1.

Table 26.1-1: Abbreviations and Acronyms

Abbreviation/Acronym	Definition
ACT	activated clotting time
ADE	adverse device effect
AE	adverse event
AKIN	Acute Kidney Injury Network
AO	ascending aorta
AR	aortic regurgitation
AS	aortic stenosis
AV	Atrioventricular
AVA	aortic valve area

Table 26.1-1: Abbreviations and Acronyms

Abbreviation/Acronym	Definition
AVR	aortic valve replacement
BARC	Bleeding Academic Research Consortium
BMI	body mass index
CBC	complete blood count
CPB	cardiopulmonary bypass
CRA	clinical research associate
CEC	Clinical Events Committee
CHF	congestive heart failure
CK	creatine kinase
CK-MB	creatine kinase-myoglobin band, a fraction of creatine kinase
CRC	Case Review Committee
CRO	clinical research organization
CT	computed tomography
CVA	cerebrovascular accident
DVI	Doppler velocity index
ECG	Electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EOA	effective orifice area
FCE	field clinical engineer
GCP	Good Clinical Practices
ICF	Informed Consent form
ICH	International Conference on Harmonisation
IEC/IRB	Independent Ethics Committee/Institutional Review Board
IFU	Instructions for Use
IMA	internal mammary artery
ISO	International Organization For Standardization
ITT	intention to treat
LA	left atrial
LBBB	left bundle branch block
LDH	lactate dehydrogenase
LV	left ventricle
LVEF	left ventricular ejection fraction
MACCE	major adverse cardiovascular and cerebrovascular events
MI	myocardial infarction
MR	mitral regurgitation
MRI	magnetic resonance imaging
mRS	Modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
NYHA	New York Heart Association classification
PA	pulmonary artery
PPM	permanent pacemaker

Table 26.1-1: Abbreviations and Acronyms

Abbreviation/Acronym	Definition
QOL	quality of life
RBBB	right bundle branch block
SADE	serious adverse device effect
SAE	serious adverse event
SAVR	surgical aortic valve replacement
TAVR	transcatheter aortic valve replacement
TEE	transesophageal Doppler echocardiography
TIA	transient ischemic attack
TR	tricuspid regurgitation
TTE	transthoracic Doppler echocardiography
USADE	unanticipated serious adverse device effect
URL	upper reference limit (defined as 99th percentile of normal reference range)
VARC	Valve Academic Research Consortium

26.2. *Definitions*

Terms are defined in Table 26.2-1.

Table 26.2-1: Definitions

Term	Definition
ACUTE KIDNEY INJURY (AKI) (AKIN System[51,52])	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 DEVICE EFFECT (ADE)	Adverse event related to the use of an investigational medical device Note 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. Note 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.
AORTIC	Intimal tear resulting in blood splitting the aortic media and producing a false lumen

Table 26.2-1: Definitions

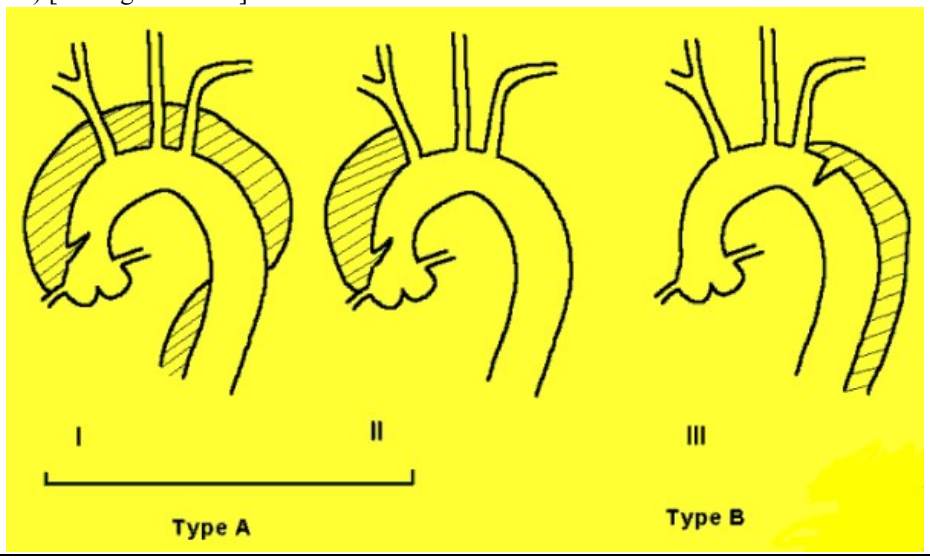
Term	Definition
DISSECTION	that can progress in an antegrade or retrograde direction Aortic dissection is further classified using Stanford classification (Types A and B depending on whether ascending or descending aorta involved) or DeBakey classification (Types I, II and III) [see Figure below]. 
AORTIC 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: See also definitions for conductance disturbance and permanent pacemaker.
BLEEDING[44,45]	Life-threatening or Disabling Bleeding • Fatal bleeding (Bleeding Academic Research Consortium [BARC] type 5[53,54])

Table 26.2-1: Definitions

Term	Definition
	• 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) • 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.
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 <u>Note 1</u>: High grade AV block is considered persistent if it is present every time the underlying rhythm is checked. <u>Note 2</u>: 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	Angiographic or echocardiographic evidence of a new, partial or complete, obstruction of a coronary ostium, either by the valve prosthesis itself, the native

Table 26.2-1: Definitions

Term	Definition
OBSTRUCTION	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.
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)
DEVICE DEFICIENCY	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. <u>Note 1</u>: Device deficiencies include malfunctions, use errors, and inadequate labeling.
DEVICE FAILURE	A device failure is identified whenever the criteria for device success are not met.

Table 26.2-1: Definitions

Term	Definition
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 as defined by VARC post-implant procedure. VARC 1[44] • 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[45] • 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[55] 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
	  ○ 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, 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

Table 26.2-1: Definitions

Term	Definition
	-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 the investigational valve implant for any reason.
FRAILTY	Slowness, weakness, exhaustion, wasting and malnutrition, poor endurance and inactivity, loss of independence.
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.
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)

Table 26.2-1: Definitions

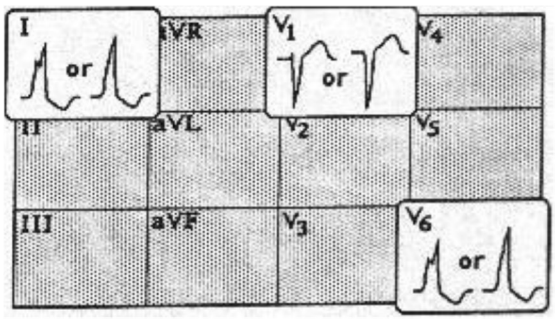
Term	Definition
	• Complications from prior surgery • Evidence of severe radiation damage (e.g. skin burns, bone destruction, muscle loss, lung fibrosis or esophageal stricture) • History of multiple recurrent pleural effusions causing internal adhesions
INTERNAL MAMMARY ARTERY OR OTHER CRITICAL CONDUIT(S) 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.
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 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-

Table 26.2-1: Definitions

<table>
<tr><th>Term</th><th>Definition</th></tr>
<tr><td></td><td>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
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[56].</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>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-</td></tr>
</table>

Table 26.2-1: Definitions

Term	Definition
	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 • 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	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 may be obtained from TEE/TTE, however, definitive diagnosis is obtained at re-operation, explant, or autopsy.
PERMANENT PACEMAKER (PPM) IMPLANTATION	Implantation of new PPM 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: PPM is implanted in subjects with new onset or worsened conduction disturbances occurring post index procedure • Not related to procedure: PPM 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, enzymatic, 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. • Conversion to open surgery • Conversion to open sternotomy during the TAVR procedure secondary to any procedure-related complications. • Unplanned use of CPB • Unplanned use of CPB for hemodynamic support at any time during the TAVR procedure.
RESPIRATORY	Inadequate ventilation or oxygenation

Table 26.2-1: Definitions

Term	Definition
INSUFFICIENCY	
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 o Anasarca o Presence of "hepato-jugular reflux" o 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)	Adverse event that led to a death
SERIOUS ADVERSE DEVICE EFFECT (SADE)	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[44,45]	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

Table 26.2-1: Definitions

Term	Definition
	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. Note 5: Assessment of the mRS score should occur at all scheduled visits in a study; mRS also should be performed after a stroke and at 90 days after the onset of any stroke.
STRUCTURAL VALVE DETERIORATION	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).
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 SERIOUS ADVERSE DEVICE EFFECT (USADE)	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
VALVE EMBOLIZATION	The valve prosthesis moves during or after deployment such that it loses contact with the aortic annulus.
VALVE	Includes valve migration, valve embolization, ectopic valve deployment, or

Table 26.2-1: Definitions

Term	Definition
MALAPPOSITION	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-RELATED SYMPTOMS/CHF REQUIRING HOSPITALIZATION	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.
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.
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

Table 26.2-1: Definitions

Term	Definition
	• 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")[57,58] 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[44]
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; CT=computed tomography; DVI=Doppler velocity index; ECG=electrocardiogram; EOA=effective orifice area; FEV= forced expiratory volume; LBBB=left bundle branch block; LV= left ventricle; MI=myocardial infarction; MRI=magnetic resonance imaging; NYHA=New York Heart Association; PPM=permanent pacemaker; RBC=red blood cell; SADE=serious adverse device effect; SAE=serious adverse event; 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

27. Appendices

27.1. *Changes in Protocol Versions*

27.1.1. Protocol Version AA to Version AB

Table 27.1-1 lists changes between protocol versions AA and AB.

Table 27.1-1: Table of Changes for Protocol Version AB (Compared to Protocol Version AA)

Section Modified	Text as Written in Protocol Version AA	Text as Written in Protocol Version AB	Justification for Modification
Page 2 Date of Amendment(s)	N/A	03 October 2014	Date of protocol amendment
Section 2 Protocol Synopsis & Section 8.1 Justification for Study Design	"…consecutive subjects will be enrolled at up to 50 study centers…"	"…consecutive subjects will be enrolled at up to 60 study centers…"	Number of centers increased to 60
Section 27 Appendices	N/A	Section 27 Appendices	New section includes summary of changes in protocol versions