REPRISE IV: REpositionable Percutaneous Replacement of Stenotic Aortic Valve through Implantation of LOTUS *Edge* Valve System in IntermediatE Surgical Risk Subjects

REPRISE IV

S2354

CLINICAL INVESTIGATION PLAN

National Clinical Trial Identification Number: NCT03618095

Sponsor:	Boston Scientific Corporation 300 Boston Scientific Way Marlborough, MA 01752 USA Australian Representative Boston Scientific Pty. Ltd. Building 1, Level 6 191 O'Riordan Street Mascot, NSW 2020, Australia

Contact Information

Role	Contact
Clinical Contacts	Laoti Bussone Senior Clinical Trial Manager, Interventional Cardiology Boston Scientific Corporation 100 Boston Scientific Way, Marlborough, MA 01752 USA Arjun M. Bhat Clinical Trial Manager, Structural Heart – Interventional Cardiology Boston Scientific Corporation 100 Boston Scientific Way, Marlborough, MA 01752 USA Blessie Concepcion Director, Clinical Trials, Structural Heart – Interventional Cardiology Boston Scientific Corporation 160 Knowles Drive, Los Gatos, CA 95032 USA
Coordinating Principal Investigators	*Interventional Cardiologist Study Co-Principal Investigator* Christopher U. Meduri, MD, MPH Piedmont Heart Institute 95 Collier Road Northwest, Suite 5015, Atlanta, GA 30309 *Cardiac Surgeon Study Co-Principal Investigator* Vinod H. Thourani, MD MedStar Heart & Vascular Institute MedStar Washington Hospital Center 110 Irving St NW, Washington, DC 20010 USA *Bicuspid Registry – Coordinating Principal Investigator* Vivek Rajagopal, MD Piedmont Heart Institute 95 Collier Road Northwest, Suite 5015, Atlanta, GA 30309 USA

Original Release: 16-Nov-2016
Current Version: 29-Apr-2020

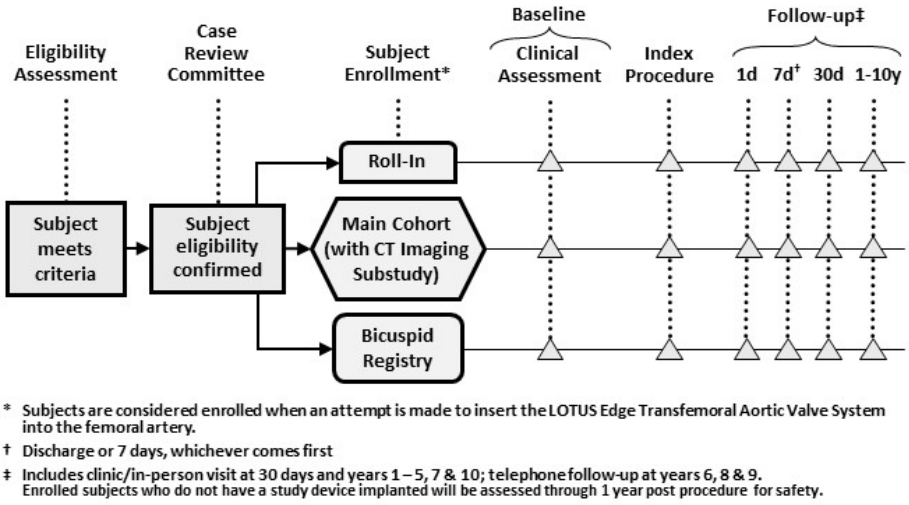
Revision History

Revision Number	Release Date	Template Version	Reason for Change
A	16-Nov-2016	90702637 Rev/Ver AG	Not Applicable
B	15-Feb-2017	90702637 Rev/Ver AG	See **Table 26.1-1**
C	23-Sep-2018	90702637 Rev/Ver AG	
D	21-Nov-2018	90702637 Rev/Ver AG	
E	25-Feb-2020	90702637 Rev/Ver AG	
F	29-Apr-2020	90702637 Rev/Ver AL	

2. Protocol Synopsis

REPRISE IV: REpositionable Percutaneous Replacement of Stenotic Aortic Valve through Implantation of LOTUS *Edge*™ Valve System in IntermediatE Surgical Risk Subjects	
Study Objective(s)	To evaluate safety and effectiveness of the LOTUS *Edge*™ Valve System when used with the Lotus™ or iSleeve™ Introducer Sets for transcatheter aortic valve replacement (TAVR) in symptomatic subjects with severe aortic stenosis who are considered at intermediate risk for surgical valve replacement including those who have a bicuspid native valve.
Intended Use	The LOTUS *Edge* Valve System is intended to improve aortic valve function in symptomatic subjects with severe aortic stenosis who are at intermediate risk for standard surgical aortic valve replacement (SAVR), including those who have a bicuspid native valve. The iSleeve and Lotus Introducer Sets are intended to provide percutaneous access to the vascular system.
Test Device(s) and Sizes	REPRISE IV uses the following investigational device. **Device Name/Size** / **Description** LOTUS *Edge* Valve System Valve diameter: - 23mm - 25mm - 27mm Includes 2 main components: - a bioprosthetic bovine pericardial aortic valve (similar to the Lotus™ Valve System used in the REPRISE III IDE study [NCT02202434] and the RESPOND post-market surveillance study [NCT02031302]) - a next generation delivery system designed to increase flexibility, trackability, and coaxial alignment The LOTUS *Edge* Valve System is introduced percutaneously via the femoral artery. The iSleeve™ Introducer Set (iSleeve) and the large Lotus Introducer Set (LIS-L) can be used as accessories to facilitate vascular introduction and deployment of the LOTUS *Edge* Valve System (23mm, 25mm, and 27mm valve sizes). The iSleeve has an expandable sheath component and a dilator enabling access to transfemoral arteries ≥5.9 mm. The LIS-L is intended for use in subjects with femoral vascular access ≥6.5 mm. In countries where the introducer sets are approved, the commercial devices

REPRISE IV: REpositionable Percutaneous Replacement of Stenotic Aortic Valve through Implantation of LOTUS *Edge*™ Valve System in IntermediatE Surgical Risk Subjects	
	will be used. In countries where they are not approved, they will be considered investigational devices.
Comparator	For the primary endpoint, a performance goal (PG) based on 1-year TAVR outcomes derived from published literature will be used as the comparator for analysis.
Study Design	REPRISE IV is a prospective, multicenter single-arm study designed to evaluate the safety and effectiveness of the LOTUS *Edge* Valve System for TAVR in symptomatic subjects who have severe native aortic stenosis and are considered at intermediate risk for surgical valve replacement. Study cohorts include the following. • **Main Cohort:** A prospective, multicenter, single-arm cohort of subjects with severe aortic stenosis who are considered at intermediate risk for surgical aortic valve replacement and are treated with the LOTUS *Edge* Valve System. o **CT Imaging Substudy:** Selected centers with the ability to perform high quality 4D computed tomography (CT) scans will include subjects from the Main Cohort in a CT imaging substudy to assess the prevalence of reduced leaflet mobility and its relationship, if any, to clinical events. • **Bicuspid Nested Registry:** A prospective, single-arm, nested registry cohort of subjects who have a native bicuspid aortic valve, are considered at intermediate risk for surgical aortic valve replacement and are treated with the LOTUS *Edge* Valve System. • **Roll-In Cohort:** A roll-in phase with the study device for centers that do not have implantation experience with the LOTUS *Edge* Valve System; each of these centers will perform at least 2 roll-in cases before commencing enrollment in the evaluable Main Cohort and Bicuspid Nested Registry. Data from roll-in subjects will be summarized separately from the evaluable Main Cohort and Bicuspid Nested Registry. Roll-in subjects will not be included in the primary endpoint analysis. The REPRISE IV study will be conducted in accordance with 21 CFR Parts 11, 50, and 54; the relevant parts of the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practices (GCP); the International Standard ISO 14155 Clinical Investigation of Medical

REPRISE IV: REpositionable Percutaneous Replacement of Stenotic Aortic Valve through Implantation of LOTUS *Edge*™ Valve System in IntermediatE Surgical Risk Subjects	
	Devices for Human Subjects – Good Clinical Practice; ethical principles that have their origins in the Declaration of Helsinki; and pertinent individual country/state/local laws and regulations. The study shall not begin until the required approval/favorable opinion from the Institutional Review Board/Human Research Ethics Committee (IRB/HREC) and/or regulatory authority has been obtained, if appropriate. The study design is summarized in the figure below.  * Subjects are considered enrolled when an attempt is made to insert the LOTUS Edge Transfemoral Aortic Valve System into the femoral artery. † Discharge or 7 days, whichever comes first ‡ Includes clinic/in-person visit at 30 days and years 1 – 5, 7 & 10; telephone follow-up at years 6, 8 & 9. Enrolled subjects who do not have a study device implanted will be assessed through 1 year post procedure for safety. **REPRISE IV Study Design Overview**
Planned Number of Subjects/ Investigational Centers/ Countries	Subjects will be enrolled at up to 65 centers in the United States and Australia. There will be up to 926 subjects enrolled in REPRISE IV as shown below. **Cohort** / **Number of Subjects** Main / 696* Bicuspid Nested Registry / 100 Roll-In / Up to 130 * Up to 200 subjects from the main cohort will be enrolled in the CT Imaging Substudy. If 200 subjects have not enrolled in the CT Imaging Substudy by completion of enrollment in the main cohort, additional subjects who meet the REPRISE IV eligibility criteria will be enrolled in a separate CT Imaging Cohort to achieve a total of 200 subjects in the CT Imaging Substudy.

REPRISE IV: REpositionable Percutaneous Replacement of Stenotic Aortic Valve through Implantation of LOTUS *Edge*™ Valve System in IntermediatE Surgical Risk Subjects	
Primary Endpoint	Composite of all-cause mortality and all stroke at 1 year.
Additional Measurements	Additional measurements based on the VARC[a] endpoints and definitions will be collected peri- and post-procedure, at discharge or 7 days post-procedure (whichever comes first), 30 days, and annually through 10 years post index procedure, unless otherwise specified below. • Safety endpoints adjudicated by an independent Clinical Events Committee (CEC): o Mortality: all-cause, 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) and major (through 5 years) o Acute kidney injury (≤7 days post index procedure): based on the AKIN System Stage 3 (including renal replacement therapy) or Stage 2 o Major vascular complication (through 5 years) 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 o New onset of atrial fibrillation or atrial flutter o Coronary obstruction: periprocedural (≤72 hours post index procedure) o Ventricular septal perforation: periprocedural (≤72 hours post index procedure) o Mitral apparatus damage: periprocedural (≤72 hours post index procedure) o Cardiac tamponade: periprocedural (≤72 hours post index procedure)

REPRISE IV: REpositionable Percutaneous Replacement of Stenotic Aortic Valve through Implantation of LOTUS *Edge*™ Valve System in IntermediatE Surgical Risk Subjects	
	○ Prosthetic aortic valve malpositioning, including valve migration, valve embolization, or ectopic valve deployment ○ Transcatheter aortic valve (TAV)-in-TAV deployment ○ Prosthetic aortic valve thrombosis ○ Prosthetic aortic valve endocarditis • Device Performance endpoints peri- and post-procedure: ○ Successful vascular access, delivery and deployment of the study valve, and successful retrieval of the delivery system ○ Successful retrieval of the study valve if retrieval is attempted ○ Successful repositioning of the study valve if repositioning is attempted (see **Note 1** below) ○ Grade of aortic valve regurgitation: paravalvular, central, and combined • Device success, defined as absence of procedural mortality, correct positioning of a single valve into the proper anatomical location, intended performance of the study device (effective orifice area [EOA] >0.9 cm^2 for BSA <1.6 m^2 and EOA >1.1 cm^2 for BSA ≥1.6 m^2 plus either a mean aortic valve gradient <20 mm Hg or a peak velocity <3m/sec, and no moderate or severe prosthetic valve aortic regurgitation) • Additional indications of prosthetic aortic valve performance as measured by transthoracic echocardiography (TTE; see **Note 2** and **Note 3** below) and assessed by an independent core laboratory, including effective orifice area, mean and peak aortic gradients, peak aortic velocity, and grade of aortic regurgitation • Functional status as evaluated by the following: ○ 5-m gait speed test (at 1 year compared to baseline) ○ New York Heart Association (NYHA) classification (see **Note 3** below) • Neurological status as determined by the following: ○ National Institutes of Health Stroke Scale (NIHSS) and modified Rankin Scale (mRS) assessments, which must be performed at baseline and pre-specified timepoints for all enrolled subjects (see **Note 4** below). NIHSS and mRS must be performed by a neurology professional or certified personnel.

REPRISE IV: REpositionable Percutaneous Replacement of Stenotic Aortic Valve through Implantation of LOTUS *Edge*™ Valve System in IntermediatE Surgical Risk Subjects	
	○ For subjects diagnosed with a stroke, a neurological physical exam, mRS, and NIHSS must be performed after the event; mRS must also be administered at 90±14 days following a stroke; the simplified mRS questionnaire may be used for this follow-up assessment. The neurological physical exam must be conducted by a neurologist, neurology fellow, neurology physician assistant, or neurology nurse practitioner. • Health status as evaluated by Kansas City Cardiomyopathy and SF-12 Quality of Life questionnaires at baseline, 1 month, and 1 and 5 years. • For subjects in the Bicuspid Nested Registry, a CT scan at 30 days post LOTUS Edge Valve implantation. The data will be evaluated by an independent CT core laboratory. • For subjects in the CT Imaging Substudy, a 4D CT scan at 30 days and at 1 year post LOTUS *Edge* valve implantation to assess the prevalence of reduced leaflet mobility and its relationship, if any, to clinical events. The data will be evaluated by an independent CT core laboratory. **Note 1:** For the LOTUS *Edge* valve, repositioning may be achieved with partial or full resheathing of the valve. **Note 2:** At least 1 echocardiogram must be obtained before discharge or 7 days (whichever comes first); if multiple echocardiographic studies are performed prior to discharge and within 7 days of the procedure, the latest study performed will be used for analysis. **Note 3:** Echocardiography and NYHA assessment are not required in years 6, 8, and 9 (telephone follow-up only). **Note 4:** NIHSS is required at discharge and 1 year; mRS is required at all follow-up visits up to 5 years. a: Leon M, *et al. J Am Coll Cardiol.* 2011;57:253–69 Kappetein AP, *et al*. *J Am Coll Cardiol*. 2012;60:1438–54
Method of Assigning Subjects to Treatment	**Main Cohort:** Subjects with severe aortic valve stenosis who meet all eligibility criteria may be treated with the LOTUS *Edge* Valve System. - Up to 200 subjects from the main cohort will be enrolled in the CT Imaging Substudy. If 200 subjects have not enrolled in the CT Imaging Substudy by completion of enrollment in the main cohort, additional subjects who meet the REPRISE IV eligibility criteria

REPRISE IV: REpositionable Percutaneous Replacement of Stenotic Aortic Valve through Implantation of LOTUS *Edge*™ Valve System in IntermediatE Surgical Risk Subjects	
	will be enrolled in a separate CT Imaging Cohort to achieve a total of 200 subjects in the CT Imaging Substudy. **Bicuspid Nested Registry:** Subjects with a native bicuspid aortic valve who meet all inclusion criteria and have no other exclusion criterion may be treated with the LOTUS *Edge* Valve System as part of a single-arm, nested registry cohort. **Roll-In Cohort:** For centers that do not have implantation experience with the LOTUS *Edge* Valve System 2 to 4 roll-in subjects will be treated before commencing enrollment in the Main Cohort and Bicuspid Nested Registry.
Follow-up Schedule	All subjects implanted with a study device will be assessed at baseline, peri- and post-procedure, at discharge or 7 days post-procedure (whichever comes first), 30 days, 1 year, and then annually for up to 10 years post-procedure. Subjects who are enrolled but not implanted with a study device at the time of the procedure will be followed for safety through 1 year. The visits at 30 days, 1−5 years, 7 years, and 10 years are to be an office/clinical or in-person visit but may be done in-hospital should the subject be admitted at the time. Telephone follow-up is allowed at 6, 8, and 9 years. Procedures at each scheduled visit are described above under "Additional Measurements."
Study Duration	Subjects implanted with a study device will be followed for 10 years after the index procedure. Enrollment is expected to be completed in approximately 24 months; therefore, the total study duration is estimated to be approximately 12 years.
Participant Duration	The study duration for each subject is expected to be approximately 10 years.
Adjunctive Pharmacologic Therapy	**Anticoagulant Therapy** Anticoagulant therapy (e.g., unfractionated heparin) per local standard of care must be administered during the implant procedure, with a recommended target activated clotting time of ≥250 seconds during the index procedure.

REPRISE IV: REpositionable Percutaneous Replacement of Stenotic Aortic Valve through Implantation of LOTUS *Edge*™ Valve System in IntermediatE Surgical Risk Subjects	
	Anti-Platelet Therapy Per society guidelines[b], antiplatelet therapy with aspirin and/or a $P2Y_{12}$ inhibitor (clopidogrel recommended) is recommended after TAVR to decrease the risk of thrombotic or thromboembolic complications if there are no contraindications to these medications. Study subjects must receive some antiplatelet therapy (aspirin and/or a $P2Y_{12}$ inhibitor) for at least 1 month following valve implant. A loading dose of the same antiplatelet medication (aspirin and/or a $P2Y_{12}$ inhibitor) is required for subjects who have not been on the antiplatelet therapy for ≥72 hours at the time of the index procedure (see below for recommended doses). **Note 5:** It is recommended that subjects be treated with both aspirin and a $P2Y_{12}$ inhibitor for at least 1 month after valve implantation. Aspirin Dose The recommended loading dose of aspirin is 75–325 mg for subjects who have not been on aspirin therapy for ≥72 hours at the time of the index procedure. The loading dose must be administered prior to the implant procedure. Subjects who have been taking aspirin daily for ≥72 hours at the time of the index procedure do not require a loading dose of aspirin. After the valve implant procedure, the recommended dose of aspirin is ≥75 mg daily given for at least 1 month. It is recommended that daily aspirin be given indefinitely thereafter as per local standard of care. $P2Y_{12}$ Inhibitor Dose (clopidogrel recommended) The recommended loading dose of a $P2Y_{12}$ inhibitor is ≥300 mg clopidogrel, 60 mg prasugrel, or 180 mg ticagrelor for subjects who have not been on $P2Y_{12}$ inhibitor therapy for ≥72 hours at the time of the index procedure. The loading dose must be administered prior to the implant procedure. Subjects who have been taking a $P2Y_{12}$ inhibitor daily for ≥72 hours at the time of the index procedure do not require a loading dose of the $P2Y_{12}$ inhibitor. After the valve implant procedure, $P2Y_{12}$ inhibitor dosing per local standard of care is recommended for at least 1 month (clopidogrel is recommended with a dose of 75 mg daily). **Note 6:** If a subject requires chronic anticoagulation, either a $P2Y_{12}$ inhibitor (clopidogrel recommended) or aspirin is recommended prior to

REPRISE IV: REpositionable Percutaneous Replacement of Stenotic Aortic Valve through Implantation of LOTUS *Edge*™ Valve System in IntermediatE Surgical Risk Subjects	
	and after the implant procedure in addition to the anticoagulant therapy (but both aspirin and a $P2Y_{12}$ inhibitor are not recommended). After the implant procedure, the subject should be treated with an oral anticoagulant (warfarin or another vitamin K antagonist recommended) and either a $P2Y_{12}$ inhibitor (clopidogrel recommended) or aspirin for at least 1 month. b: Holmes DR, et al. *J Am Coll Cardiol*. 2012;59:1200–1254 Nishimura R, et al. *J Am Coll Cardiol*. 2014;63: e57–e185 Nishimura R, et al. *Circulation.* 2017;135:e1159–e95
Inclusion Criteria	IC1. Subject has documented severe aortic stenosis defined as initial AVA ≤1.0 cm^2 (or AVA index ≤0.6 cm^2/m^2) AND a mean pressure gradient ≥40 mm Hg OR maximal aortic valve velocity ≥4.0 m/s OR Doppler velocity index ≤0.25 as measured by echocardiography and/or invasive hemodynamics[c,d] **Note 7:** In cases of low flow, low gradient aortic stenosis with left ventricular dysfunction (ejection fraction <50%), dobutamine can be used to assess the grade of aortic stenosis (maximum dobutamine dose of 20 mcg/kg/min recommended)[c]; the subject may be enrolled if echocardiographic criteria are met with this augmentation. IC2. A subject in the Bicuspid Aortic Valve Nested Registry cohort must have a documented Sievers Type 0 or Sievers Type 1 bicuspid aortic valve based on CT assessment and confirmed by the CT core lab with hemodynamic parameters that meet the criteria in IC1. IC3. Subject has a documented aortic annulus size of ≥20 mm and ≤27 mm based on the center's assessment of pre-procedure diagnostic imaging (and confirmed by the Case Review Committee [CRC]). IC4. Subject has symptomatic aortic valve stenosis per IC1 definition above with NYHA Functional Class ≥ II. IC5. Heart team (which must include an experienced cardiac interventionalist and an experienced cardiac surgeon) agrees that the subject is at intermediate risk of operative mortality (≥3% and <8% at 30 days based on the Society of Thoracic Surgeons [STS]

REPRISE IV: REpositionable Percutaneous Replacement of Stenotic Aortic Valve through Implantation of LOTUS *Edge*™ Valve System in IntermediatE Surgical Risk Subjects	
	risk score and other clinical comorbidities unmeasured by the risk calculator) and TAVR is appropriate. **Note 8:** Risk of operative mortality must be assessed via an in-person evaluation by a center cardiac surgeon and must be confirmed by the CRC (which must include an experienced cardiac surgeon). IC6. Heart team agrees that the subject is likely to benefit from valve replacement. IC7. Subject (or legal representative) has been informed of the study requirements and the treatment procedures and provides written informed consent. IC8. Subject, family member, and/or legal representative agree(s) and subject is capable of returning to the study hospital for all required scheduled follow-up visits. IC9. Subject is expected to be able to take the protocol-required adjunctive pharmacologic therapy. c: Nishimura RA, et al. *J Am Coll Cardiol*. 2014;63:e57–e185 d: Leon M, *et al. J Am Coll Cardiol.* 2011;57: 253–69
Exclusion Criteria	EC1. Subject has a unicuspid or bicuspid aortic valve (not applicable to subjects in the Bicuspid Nested Registry cohort). **Note 9:** Subjects in the Bicuspid Nested Registry cohort will have a documented Sievers Type 0 or Sievers Type 1 bicuspid aortic valve based on CT assessment and confirmed by the CT core lab. Subjects are not eligible for inclusion in the Bicuspid Nested Registry cohort if the maximum diameter of the ascending aorta is >45 mm or if the subject has another indication for aortic root replacement. Subjects with a Sievers Type 2 bicuspid valve are not eligible for enrollment in any study cohort. EC2. Subject has had an acute myocardial infarction within 30 days prior to the index procedure (defined as Q-wave MI or non–Q-wave MI with total CK elevation ≥ twice normal in the presence of CK-MB elevation and/or troponin elevation).

REPRISE IV: REpositionable Percutaneous Replacement of Stenotic Aortic Valve through Implantation of LOTUS *Edge*™ Valve System in IntermediatE Surgical Risk Subjects	
	EC3. Subject has had a cerebrovascular accident or transient ischemic attack clinically confirmed by a neurologist or neuroimaging within the past 6 months prior to study enrollment. EC4. Subject is on renal replacement therapy or has GFR <20 (based on hospital preferred method). See AEC1 below if subject is in the CT Imaging Substudy. EC5. Subject has a pre-existing prosthetic aortic or mitral valve. EC6. Subject has severe (4+) aortic, tricuspid, or mitral regurgitation. EC7. Subject has moderate to severe mitral stenosis (mitral valve area ≤1.5 cm^2 and diastolic pressure half-time ≥150 ms, Stage C or D[c]). EC8. Subject has a need for emergency surgery for any reason. EC9. Subject has a history of endocarditis within 6 months of index procedure or evidence of an active systemic infection or sepsis. EC10. Subject has echocardiographic evidence of new intra-cardiac vegetation or intraventricular or paravalvular thrombus requiring intervention. EC11. Subject has platelet count <50,000 cells/mm^3 or >700,000 cells/mm^3, or white blood cell count <1,000 cells/mm^3. EC12. Subject will refuse transfusions or has had a gastrointestinal bleed requiring hospitalization or transfusion within the past 3 months or has other clinically significant bleeding diathesis or coagulopathy that would preclude treatment with required antiplatelet regimen. EC13. Subject has known hypersensitivity to contrast agents that cannot be adequately pre-medicated, or has known hypersensitivity to aspirin, all $P2Y_{12}$ inhibitors, heparin, nickel, tantalum, titanium, or polyurethanes. EC14. Subject has a life expectancy of less than 24 months due to non-cardiac, comorbid conditions based on the assessment of the investigator at the time of enrollment. EC15. Subject has hypertrophic cardiomyopathy. EC16. Subject has any therapeutic invasive cardiac or vascular procedure within 30 days prior to the index procedure (except for balloon

REPRISE IV: REpositionable Percutaneous Replacement of Stenotic Aortic Valve through Implantation of LOTUS *Edge*™ Valve System in IntermediatE Surgical Risk Subjects	
	aortic valvuloplasty or pacemaker or implantable cardioverter defibrillator implantation, which are allowed). EC17. Subject has multivessel coronary artery disease with a Syntax score >22, and/or an unprotected left main coronary artery. EC18. Subject has severe left ventricular dysfunction with ejection fraction <20%. EC19. Subject is in cardiogenic shock or has hemodynamic instability requiring inotropic support or mechanical support devices. EC20. Subject has arterial access that is not acceptable for the study device delivery system as defined in the device Instructions For Use. EC21. Subject has severe vascular disease that would preclude safe access (e.g., aneurysm with thrombus that cannot be crossed safely; marked tortuosity; significant narrowing of the abdominal aorta; severe unfolding of the thoracic aorta; or thick, protruding, ulcerated atheroma in the aortic arch). EC22. Subject has current problems with substance abuse (e.g., alcohol, etc.) that may interfere with the subject's participation in this study. EC23. Subject is participating in another investigational drug or device study that has not reached its primary endpoint. EC24. Subject has untreated conduction system disorder (e.g., Type II second degree atrioventricular block) that in the opinion of the treating physician is clinically significant and requires a pacemaker implantation. Enrollment is permissible after permanent pacemaker implantation. EC25. Subject has severe incapacitating dementia. c: Nishimura RA, et al. *J Am Coll Cardiol*. 2014;63:e57–e185
Additional Exclusion Criteria	Additional exclusion criteria apply to subjects considered for enrollment in the CT Imaging Substudy as listed below. AEC1. Subject has eGFR <30 mL/min (chronic kidney disease stage IV or stage V).

REPRISE IV: REpositionable Percutaneous Replacement of Stenotic Aortic Valve through Implantation of LOTUS *Edge*™ Valve System in IntermediatE Surgical Risk Subjects	
	AEC2. Subject has atrial fibrillation that cannot be rate controlled to ventricular response rate < 60 bpm. AEC3. Subject is expected to undergo chronic anticoagulation therapy after the index procedure. **Note 10:** Subjects treated with short-term anticoagulation post procedure can be included in the imaging substudy; in these subjects the 30-day imaging will be performed 30 days after discontinuation of anticoagulation.
Statistical Methods	
Analysis Sets	Analysis sets are listed below. - Intention-To-Treat (ITT): This population includes all subjects who sign an Informed Consent Form and are enrolled in the study, regardless of whether the study device is implanted. - Implanted: This population includes all subjects who sign an Informed Consent Form, are enrolled in the study, and are implanted with the study device. A subject is considered enrolled in the study when an attempt is made to insert a LOTUS *Edge* valve.
Primary Endpoint Statistical Hypothesis	In the Main Cohort, the rate of the primary endpoint (composite of all-cause mortality and all stroke at 1 year) is less than the performance goal (PG) of 15.2% (expected rate of 11.1% plus testing margin of 4.1%).
Statistical Test Method for the Primary Endpoint	A one-sample z-test will be used to test the one-sided hypothesis that the 1-year primary endpoint rate for LOTUS *Edge* in the Main Cohort is less than the PG: H_0: $P_{LOTUS\ Edge} \geq PG$ H_1: $P_{LOTUS\ Edge} < PG$ where $P_{LOTUS\ Edge}$ is the primary endpoint rate for the LOTUS *Edge* group and PG is the performance goal. The primary analysis set for the primary endpoint is the ITT analysis set. This endpoint will also be analyzed for the implanted analysis set.

REPRISE IV: REpositionable Percutaneous Replacement of Stenotic Aortic Valve through Implantation of LOTUS *Edge*™ Valve System in IntermediatE Surgical Risk Subjects	
Sample Size Parameters for the Primary Endpoint	The sample size calculation for the primary endpoint (composite of all-cause mortality and all stroke at 1 year) is based on the following assumptions. • Expected rate for LOTUS *Edge* = 11.1%† • Testing margin = 4.1% (37% relative to the expected rate) • Performance goal (PG) = 15.2% (expected rate of 11.1% plus testing margin of 4.1%) • Test significance level (α) = 0.025 (1-sided) • Power = 87.5% • Number of evaluable subjects = 675 • Expected rate of attrition = 3% • Total enrolment (evaluable Main Cohort) = 696 subjects † Estimated pooled rate from the fixed effect model based on the TAVR arm data from PARTNER II S3i[e] and SURTAVI[f] e: Thourani VH, et al. *Lancet* 2016;387:2218-25 f: Reardon MJ, et al. N Engl J Med 2017:376:1321-31
Success Criteria for the Primary Endpoint	If the *P* value from the one-sample z-test is <0.025, it will be concluded that the primary endpoint with the LOTUS *Edge* Valve System is less than the PG. This corresponds to the one-sided upper 97.5% confidence bound of the observed composite rate of all-cause mortality and all stroke in the Main Cohort at 1 year being < 15.2%.
Bicuspid Nested Registry	The planned enrollment for the Bicuspid Nested Registry cohort is up to 100 subjects. Descriptive statistics for all endpoints will be summarized using both the ITT and implanted analysis sets.

3. Table of Contents

3.1. *Table of Figures*

3.2. *Table of Tables*

4. Introduction

This protocol specifies procedures and contains information relevant to the clinical evaluation of the LOTUS *Edge*™ Valve System, a transcatheter aortic valve replacement (TAVR) device designed and manufactured by Boston Scientific Structural Heart a Division of Boston Scientific Corporation (BSC). The LOTUS *Edge* 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 TAVR. Early leaflet function during valve deployment and the presence of a radiopaque tantalum marker on the braided frame facilitate optimal initial positioning of the valve. If needed, the valve may be partially or fully resheathed 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 regurgitation (PVR).

The LOTUS *Edge* Valve System is introduced into the body using either the iSleeve™ Introducer Set or the large Lotus Introducer Set. Both sets are designed to facilitate vascular introduction and deployment of the system. Both devices have a dilator and sheath component, but the iSleeve sheath can expand temporarily as LOTUS *Edge* is inserted through the femoral artery. This allows for an extended range of vascular access.

Additional device information can be found in Section **5**.

Study subjects will be entered into the Roll-In Cohort, single-arm Main Cohort, or a single-arm, nested registry cohort of subjects with a native bicuspid aortic valve (Bicuspid Nested Registry). Additional information on study design can be found in Section **7**.

4.1. *Background*

4.1.1. Aortic Stenosis

The incidence of aortic stenosis (AS), which most commonly occurs in the very elderly, 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[1-3]. It is estimated that nearly 5% of elderly ≥75 years of age have AS and its prevalence is expected to increase due to an aging population[2,3]. Aortic stenosis is associated with high rates of death and complications after the appearance of symptoms[2,3].

Many patients with severe and symptomatic aortic stenosis are successfully treated with surgical aortic valve replacement (SAVR), which can reduce symptoms and improve survival[2-5]. However, up to one-third of patients with severe AS are not treated with SAVR because of their comorbidities and consequent perioperative risk[6-8]. With standard medical therapy, mortality after 1 year among these patients may be as high as 50%[2,3,8]. Percutaneous transluminal aortic valvuloplasty, which was introduced as an alternative to SAVR in elderly and/or high-risk surgical patients, can provide symptomatic relief and/or temporary improvement but does not provide definitive treatment in patients with severe calcific AS. It is also associated with relatively high mortality and complication rates[3,9].

Transcatheter aortic valve replacement provides an alternative to the surgical approach in the treatment of severe AS. An antegrade (transapical) or retrograde (e.g., transfemoral, transaortic through the ascending aorta, trans-subclavian) approach can be used[10]. Patients generally undergo a joint interdisciplinary screening process, including comprehensive multimodality imaging[11-14], prior to procedure recommendation. Because of the limitations of existing surgical risk scores[15-18], center heart teams also consider other co-morbidities and patient frailty to fully characterize risk[19]. The use of TAVR has produced significant reductions in mortality and repeat hospitalization compared to medical therapy[8,20,21]. In selected high-risk surgical patients, TAVR has also resulted in similar[22-24] or lower[25-27] mortality when compared to SAVR. Continuous procedural refinements and device improvements have aimed to widen application to lower risk patients[28,29]. Propensity score analyses have suggested comparable mortality after TAVR or SAVR in some intermediate-risk patients[30-32], and 2 recent randomized, controlled trials (RCT) showed similar outcomes between the two treatment groups[33,34]. Meta-analyses have also shown similar long-term survival after TAVR compared to SAVR[35,36]. Currently, TAVR is approved for use in AS patients considered inoperable or at intermediate to high surgical risk and expert consensus documents have outlined TAVR patient selection criteria[4,5,37,38].

Recently, reduced aortic valve leaflet motion, mainly asymptomatic, has been identified with follow-up CT among some TAVR subjects[39,40]. Therapeutic anticoagulation with warfarin was associated with a decreased incidence and leaflet motion could be restored with anticoagulation. This phenomenon has not been definitively linked with abnormal clinical symptoms. Studies to assess its prevalence and determine any relationship to patient, procedural, or pharmacologic factors or clinical events are ongoing.

Table 4.1-1 summarizes outcomes at 30 days and 1 year from TAVR studies that enrolled subjects similar to those planned for this study (intermediate surgical risk, transfemoral access), as well as results from studies with inoperable and high-risk surgical patients.

Table 4.1-1: TAVR Outcomes at 30 Days and 1 Year – Transfemoral Access

Study	Device/N	All-cause Death	Disabling/ Major Stroke	Major VC	LT Bleeding	AKI
30-Day Outcomes – Randomized Studies						
PARTNER 1A[a] (2011)[22]	SAPIEN / 244[†]	3.3	2.9	14.0	9.5[b]	2.5[c]
PARTNER 2A[d] (2016)[33]	SAPIEN XT / 775*	3.0	2.3	8.5	6.7	0.5[e]
PARTNER 2B[f] (2015)[41]	SAPIEN XT / 284[†] SAPIEN / 276[†]	3.5 5.1	3.2 3.0	9.5 15.2	7.8 12.4	15.4[g] 16.8[g]
CoreValve High Risk[h] (2014)[25]	CoreValve / 390[†]	3.3	3.9	5.9	13.6	6.0[g]
NOTION[i] (2015)[42]	CoreValve / 142[‡]	2.1	1.4[j]	5.6	11.3[k]	0.7[l]
SURTAVI[m] (2017)[34]	CoreValve / 864*	2.2	1.2	6.0	12.2	1.7[l]
CHOICE[f] (2014)[43]	SAPIEN XT / 121[†] CoreValve / 117[†]	4.1 5.1	2.5 2.6	9.9 11.1	8.3[b] 12.0[b]	4.1[e] 9.4[e]

Table 4.1-1: TAVR Outcomes at 30 Days and 1 Year – Transfemoral Access

Study	Device/N	All-cause Death	Disabling/ Major Stroke	Major VC	LT Bleeding	AKI
REPRISE III[f] (2018)[44]	Lotus Valve[n] / 607[†] CoreValve[n] / 305[†]	2.5 2.3	2.0 3.3	7.0 5.3	8.0 5.0	2.5[l] 3.6[l]
30-Day Outcomes – Single-Arm Studies						
PARTNER NRCA[f] (2014)[45]	SAPIEN / 1023[†]	4.3	2.4	8.0	6.8[b]	1.6[e]
SAPIEN 3[o] (2016)[46]	SAPIEN 3 / 953* SAPIEN 3 / 491[†]	1.1 1.6	0.7 0.8	6.3 5.5	3.6 5.5	0.8[l] 1.2[l]
CoreValve Extreme Risk[p] (2014)[47]	CoreValve / 489[†]	8.4	2.3	8.2	12.7	11.8
Evolut R First in Man[q] (2015)[48]	Evolut R / 60[†]	0.0	0.0[j]	8.3	5.0	1.7[l]
EVOLUT R US Study[r] (2017)[49]	Evolut R / 241[†]	2.5	3.3	7.5	7.1	1.2[l]
PORTICO Pre-CE Mark Study[f] (2018)[50]	Portico / 222[†]	3.6	3.2	7.3	3.6	1.4[e]
1-Year Outcomes – Randomized Studies						
PARTNER 1A[a] (2011)[22]	SAPIEN / 244[†]	22.2	3.8	14.4	16.2[b]	5.1[c]
PARTNER 2A[d] (2016)[33]	SAPIEN XT / 775*	10.0	4.3	8.8	11.1	2.2[e]
PARTNER 2B[f] (2015)[41]	SAPIEN XT / 284[†] SAPIEN / 276[†]	22.3 23.3	4.8 5.5	10.3 16.1	14.1 19.9	31.0[e] 31.3[e]
CoreValve High Risk[h] (2014)[25]	CoreValve / 390[†]	14.2	5.8	6.2	16.6	6.0[g]
NOTION[i] (2015)[42]	CoreValve / 142[‡]	4.9	2.9[j]	–	–	–
SURTAVI[m] (2017)[34]	CoreValve / 864*	6.7	2.2	–	–	–
CHOICE[f] (2015)[51]	SAPIEN XT / 121[†] CoreValve / 117[†]	17.4 12.8	5.8 3.4	11.6 12.0	14.0[b] 12.8[b]	– –
REPRISE III[f] (2018)[44]	Lotus Valve[s] / 607[†] CoreValve[s] / 305[†]	11.9 13.5	3.6 7.1	7.7 6.1	9.9 9.8	2.6[l] 3.7[l]
1-Year Outcomes – Single-Arm Studies						
PARTNER NRCA[f] (2014)[45]	SAPIEN / 1023[†]	19.0	3.6	8.4	12.9[b]	3.6[e]
CoreValve Extreme Risk Pivotal[p] (2014)[47]	CoreValve / 489[†]	24.3	4.3	8.4	17.6	11.8
SAPIEN 3[t] (2016)[32]	SAPIEN 3 / 925*	6.5	1.7	–	–	–
PORTICO Pre-CE Mark Study[f] (2018)[50]	Portico / 222[†]	13.8	5.8	8.8	5.2	3.0

Table 4.1-1: TAVR Outcomes at 30 Days and 1 Year – Transfemoral Access

Study	Device/N	All-cause Death	Disabling/ Major Stroke	Major VC	LT Bleeding	AKI

Data are presented as %; N is the number of subjects with transfemoral/iliofemoral access unless indicated otherwise; † = high/extreme surgical risk; * = intermediate surgical risk; ‡ = all comers study.
The SAPIEN™, SAPIEN XT™, and SAPIEN 3™ Transcatheter Heart Valve Systems are manufactured by Edwards Lifesciences, Irvine, CA, USA. The CoreValve® and CoreValve Evolut™ R Transcatheter Aortic Valve Systems are manufactured by Medtronic Corp, Dublin, Ireland. The Lotus™ Valve System is manufactured by Boston Scientific Corporation, Marlborough, MA, USA.

a: 70% TF and 30% TA
b: Major bleeding
c: Renal replacement therapy
d: 76% TF and 24% TA
e: AKIN Stage 3 (including renal replacement therapy)
f: 100% TF
g: Modified RIFLE classification per VARC 1
h: 83% TF and 17% TAo/SC
i: 97% TF and 3% SC
j: All stroke
k: Life-threatening and major
l: AKIN Stage 2 or 3
m: 94% TF, 4% TAo, and 2% SC
n: Outcomes are for the implanted analysis sets: N=601 Lotus; N=303 CoreValve (153 CoreValve and 144 Evolut R)
o: 87% TF and 13% TA/TAo (intermediate and high risk)
p: 99% TF (1% not implanted)
q: 98% TF and 2% TAo
r: 90% TF and 10% other
s: Outcomes are shown for the Implanted analysis sets: N=587 Lotus; N=297 CoreValve
t: 88% TF and 12% TA/TAo

Abbreviations: AKI=acute kidney injury; LT=life threatening; PVR=paravalvular regurgitation; SC=subclavian; TA=transapical; TAo=trans-aortic; TAVR=transcatheter aortic valve replacement; TF=transfemoral/iliofemoral; VARC=Valve Academic Research Consortium; VC=vascular complications

Though infrequent, significant complications can occur with TAVR and subsequently impact long-term outcomes and possibly limit use in lower risk patients[52]. Precise valve positioning can be challenging, particularly in the context of markedly altered or unfolded aortic anatomy or large and eccentric calcified plaques at the aorto-ventricular interface. Under such conditions, TAVR can result in valve misplacement, embolization, the need for a second device, or coronary occlusion[53]. Placement in a heavily calcified native valve can produce an incomplete seal between the bioprosthetic valve and aortic annulus, resulting in PVR, which in turn has been associated with increased mortality in some studies[54-56]. The impact of mild PVR is less clear[57,58] although a recent meta-analysis suggested that mild PVR may also be associated with increased all-cause and cardiovascular mortality[59].

The Lotus™ Valve System was designed to address issues with earlier TAVR devices[60]. Controlled mechanical expansion and early leaflet functioning allow for precise positioning. If needed, minor repositioning is accomplished through partial valve recapture; full recapture

facilitates removal of the valve if a different valve is required. The outer seal is designed to minimize PVR. Additional device information can be found in Section **5.1**.

The safety and performance of the Lotus Valve System and the follow-on LOTUS *Edge* Valve System for TAVR in symptomatic high-risk surgical patients with severe AS are under evaluation in the REPRISE clinical program as described in Section **4.1.2**. REPRISE IV will evaluate safety and effectiveness of the LOTUS *Edge* Valve System for TAVR in intermediate-risk surgical patients, including those who have a native bicuspid aortic valve.

4.1.2. REPRISE Clinical Program

The REPRISE clinical program includes an evolving set of clinical studies intended to demonstrate the safety and performance of the Lotus Valve System. To ensure proper use and mitigate any procedural complication that could be secondary to misuse or misinterpretation of the Instructions for Use (IFU), a comprehensive training and proctorship program was implemented by BSC. Given the importance of selecting appropriate subjects, a Case Review Committee (CRC) comprised of the Principal Investigators (PI), other investigators experienced with TAVR, and the Sponsor was established to confirm subject eligibility across study centers during the trial screening process. Safety endpoints for the REPRISE studies are adjudicated independently (Clinical Events Committee [CEC] for the RCT and single-arm trials; Independent Medical Reviewer [IMR] for the postmarket study). Prosthetic valve function and cardiac function endpoints are assessed by independent echocardiography and electrocardiography core labs. Clinical endpoint definitions and pre-specified follow-up measurements are based on Valve Academic Research Consortium (VARC) metrics[61,62]. The Lotus Valve System is evaluated in the single-arm REPRISE I (ClinicalTrials.gov Identifier NCT01383720), REPRISE II (NCT01627691), and REPRISE Japan (NCT02491255) trials; the REPRISE III (NCT02202434) RCT; and the RESPOND (NCT02031302) postmarket safety surveillance study. The LOTUS Edge Valve System and the iSleeve Introducer Set are evaluated in the single-arm REPRISE NG DS (NCT02329496) and REPRISE EDGE (NCT02854319) studies.

Described below are results from studies that have reached their primary endpoints.

4.1.2.1. REPRISE I Study

The prospective, single arm, multicenter REPRISE I (REpositionable Percutaneous Replacement of Stenotic Aortic Valve through Implantation of Lotus™ Valve SystEm; NCT01383720) feasibility study (N=11) assessed the acute safety and performance of the Lotus Valve System in symptomatic subjects with calcific aortic stenosis who were considered high risk for surgical valve replacement[63]. The primary endpoint was clinical procedural success, defined as successful implantation of a Lotus Valve (per the VARC-1 definitions[61]) 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.

The primary endpoint was achieved in 9/11 subjects[63]. The device was successfully implanted in all 11 subjects but there was a device failure in 1 subject based on a mean gradient of 22 mmHg. Ten (10) of 11 subjects had no in-hospital MACCE; there were no deaths and 1 major stroke. At discharge TTE, PVR was mild in 2 subjects, trivial in 1 subject, and absent in the other 8 subjects. **Table 4.1-2** shows clinical and echocardiographic outcomes to the end of the study (5 years). Valve function was excellent with minimal PVR and low clinical event rates. The results of the REPRISE I feasibility study support the safety and performance of the Lotus Valve System.

Table 4.1-2: Outcomes to 5 Years in REPRISE I

Outcomes	30 Days	1 Year	2 Years	3 Years	4 Years	5 Years
Clinical Outcomes (CEC Adjudicated, VARC Definitions)						
All-cause mortality	0.0 (0/11)	0.0 (0/11)	0.0 (0/11)	9.1 (1/11)	27.3 (3/11)	36.4 (4/11)
Cardiovascular	0.0 (0/11)	0.0 (0/11)	0.0 (0/11)	0.0 (0/11)	9.1 (1/11)	9.1 (1/11)
All stroke	9.1 (1/11)	9.1 (1/11)	9.1 (1/11)	18.2 (2/11)	18.2 (2/11)	18. (2/11)
Major stroke	9.1 (1/11)	9.1 (1/11)	9.1 (1/11)	9.1 (1/11)	9.1 (1/11)	9.1 (1/11)
Major vascular complications	9.1 (1/11)	9.1 (1/11)	9.1 (1/11)	9.1 (1/11)	9.1 (1/11)	9.1 (1/11)
Life-threatening/disabling bleeding	18.2 (2/11)	18.2 (2/11)	18.2 (2/11)	18.2 (2/11)	18.2 (2/11)	18.2 (2/11)
Major bleeding	18.2 (2/11)	18.2 (2/11)	27.3 (3/11)	27.3 (3/11)	27.3 (3/11)	27.3 (3/11)
AKI – Stage 2/3	0.0 (0/11)	0.0 (0/11)	0.0 (0/11)	0.0 (0/11)	0.0 (0/11)	0.0 (0/11)
New PPM[a]	36.4 (4/11)	36.4 (4/11)	36.4 (4/11)	36.4 (4/11)	36.4 (4/11)	36.4 (4/11)
Myocardial infarction	0.0 (0/11)	0.0 (0/11)	0.0 (0/11)	0.0 (0/11)	0.0 (0/11)	9.1 (1/11)
Valve-related dysfunction[c]	0.0 (0/11)	0.0 (0/11)	0.0 (0/11)	0.0 (0/11)	0.0 (0/11)	0.0 (0/11)
Hospitalization[d]	0.0 (0/11)	0.0 (0/11)	0.0 (0/11)	0.0 (0/11)	0.0 (0/11)	0.0 (0/11)
TAV-in-TAV	0.0 (0/11)	0.0 (0/11)	0.0 (0/11)	0.0 (0/11)	0.0 (0/11)	0.0 (0/11)
Valve thrombosis	0.0 (0/11)	0.0 (0/11)	0.0 (0/11)	0.0 (0/11)	0.0 (0/11)	0.0 (0/11)
Endocarditis	0.0 (0/11)	0.0 (0/11)	0.0 (0/11)	0.0 (0/11)	0.0 (0/11)	0.0 (0/11)
Aortic Valve Performance by Transthoracic Echocardiography (Core Lab Assessment)						
EOA (cm^2)[e]	1.59±0.14 (11)	1.51±0.22 (11)	1.51±0.19 (11)	1.56±0.23 (8)	1.55±0.21 (7)	1.55±0.37 (5)
Mean gradient (mmHg)[f]	11.7±3.0 (11)	15.4±4.6 (11)	15.5±4.4 (11)	15.6±4.4 (8)	15.6±4.6 (7)	14.1±4.1 (6)
Paravalvular Aortic Regurgitation						
None	9.1 (1/11)	9.1 (1/11)	81.8 (9/11)	87.5 (7/8)	100 (7/7)	80.0 (4/5)
Trace/trivial	0.0 (0/11)	9.1 (1/11)	9.1 (1/11)	0.0 (0/8)	0.0 (0/7)	20.0 (1/5)
Mild	18.2 (2/11)	9.1 (1/11)	9.1 (1/11)	12.5 (1/8)	0.0 (0/7)	0.0 (0/5)
Moderate or Severe	0.0 (0/11)	0.0 (0/8)	0.0 (0/11)	0.0 (0/8)	0.0 (0/7)	0.0 (0/5)
New York Heart Association Class[g]						
Class I	27.3 (3/11)	45.5 (5/11)	54.5 (6/11)	62.5 (5/8)	57.1 (4/7)	66.7 (4/6)
Class II	63.6 (7/11)	54.5 (6/11)	45.5 (5/11)	12.5 (1/8)	14.3 (1/7)	16.6 (1/6)
Class III	9.1 (1/11)	0.0 (0/11)	0.0 (0/11)	25.0 (2/8)	28.6 (2/7)	16.6 (1/6)
Class IV	0.0 (0/11)	0.0 (0/11)	0.0 (0/11)	0.0 (0/8)	0.0 (0/7)	0.0 (0/6)

Numbers are presented as % (count/sample size) or mean±SD (n)

a: Resulting from new or worsened conduction disturbances

b: Periprocedural

c: Requiring repeat procedure (surgical/interventional)

d: For valve-related symptoms or worsening congestive heart failure

Table 4.1-2: Outcomes to 5 Years in REPRISE I

Outcomes	30 Days	1 Year	2 Years	3 Years	4 Years	5 Years

e: Baseline effective orifice area (cm^2): 0.68 ± 0.19 (11); change from baseline is significant at all time points
f: Baseline mean aortic gradient (mmHg): 53.9±20.9 (11); change from baseline is significant at all time points
g: At baseline, 6 subjects were considered Class II and 5 subjects were considered Class III.
Abbreviations: AKI=acute kidney injury; CEC=clinical events committee; EOA=effective orifice area; TAV=transcatheter aortic valve; VARC=Valve Academic Research Consortium
References: Meredith 2014[63]; Gooley 2018[64]

4.1.2.2. REPRISE II Study

The REpositionable Percutaneous Replacement of Stenotic Aortic Valve through Implantation of Lotus™ Valve System – Evaluation of Safety and Performance (REPRISE II; NCT01627691) clinical trial was designed to evaluate the safety and performance of the Lotus Valve System for TAVR in symptomatic subjects with calcific stenotic aortic valves who were considered high risk for SAVR. This prospective, single-arm, multicenter, CE-Mark study enrolled 120 subjects in the main cohort at 14 investigative centers in Australia, France, Germany and the United Kingdom. Clinical follow-up will extend through 5 years.

The primary device performance endpoint was the mean aortic valve pressure gradient at 30 days post implant as measured by echocardiography. This endpoint was analyzed on an as-treated (subjects who received the Lotus Valve) basis. A one-sample *t*-test was used to test the one-sided hypothesis that the primary device performance endpoint is less than the prespecified performance goal (PG) of 18 mmHg. Two interim analyses were conducted on the first 40 and 60 subjects; the alpha-adjustment for multiple comparisons[65] was 0.01123 and 0.00792, respectively. The alpha level adjustment for the final analysis conducted on the fully enrolled cohort of 120 subjects was 0.01305. The primary safety endpoint was all-cause mortality at 30 days after the implant procedure and was evaluated on an intention-to-treat (ITT; all subjects enrolled, whether or not a study device is implanted) basis.

The 30-day mean aortic valve pressure gradient was 11.45±5.20 mmHg with a one-sided 98.695% upper confidence bound of 12.64. The *P* value from the one-sample *t*-test was <0.0001 and so the Lotus Valve was concluded to have a 30-day mean aortic pressure gradient <18 mmHg and the primary device performance endpoint was met. **Table 4.1-3** shows device performance endpoints[66]. Successful vascular access, delivery and deployment of the Lotus Valve along with successful retrieval of the delivery system was achieved in all 120 subjects. Repositioning and/or retrieval was successful in all patients in whom it was attempted. **Table 4.1-4** shows 30-day, 1-year, 2-year, 3-year, 4-year, and 5-year clinical and echocardiographic outcomes. Mortality at 30 days, 1 year, and 5 years was 4.2%, 11.0%, and 42.6%, respectively; the disabling stroke rate was 1.7%, 3.5%, and 7.0%. Mean aortic valve pressure gradient remained low at 12.58±5.66 mmHg (1 year) and 14.43±6.44 mmHg (5 years). There were no repeat procedures for valve-related dysfunction through 5 years. Core lab assessment of PVR at 30 days indicated no severe regurgitation and 1 case of moderate regurgitation; in 83.3% (80/96) of subjects there was trace/trivial or no PVR. The low PVR rate observed at 30 days was maintained at 1 year (89% with none/trivial PVR) and

out to 5 years (80%with none/trivial PVR). The observed clinical results are consistent with other TAVR studies (see **Table 4.1-1**) and the rates of PVR are lower[8,22,25,32,41,43,46-48,51]. The results of the REPRISE II study support the safety and performance of the Lotus Valve System.

Table 4.1-3: Device Performance Endpoints – REPRISE II Main Cohort

Outcomes	REPRISE II
Successful vascular access, delivery, and deployment of the Lotus Valve System, and successful retrieval of the delivery system	100.0% (120/120)
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 for the last valve attempted	100.0% (32/32)
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% (6/6)

Values are % (count/sample size)
Reference: Meredith 2014[66]

Table 4.1-4: Clinical and Echocardiographic Outcomes to 5 Years – REPRISE II Main Cohort (N=120)

Outcomes	30 Days	1 Year	2 Years	3 Years	4 Years	5 Years
Clinical Outcomes (CEC Adjudicated, VARC Definitions)						
All-cause mortality	4.2 (5/119)	11.0 (13)	16.9 (20)	23.1 (27)	30.8 (36)	42.6 (50)
Cardiovascular	4.2 (5/119)	6.7 (8)	10.4 (12)	12.3 (14)	16.3 (18)	24.0 (25)
Stroke	6.1 (7/115)	9.5 (11)	9.5 (11)	10.5 (12)	10.5 (12)	13.0 (14)
Disabling stroke	1.7 (2/115)	3.5 (4)	3.5 (4)	4.5 (5)	4.5 (5)	7.0 (7)
Major vascular complications	2.6 (3/116)	2.5 (3)	2.5 (3)	2.5 (3)	2.5 (3)	2.5 (3)
New PPM[a]	29.1(34/117)	32.2 (38)	34.2 (40)	35.4 (41)	35.3 (41)	36.4 (42)
Life-threatening/disabling bleeding	5.1 (6/117)	5.9 (7)	7.8 (9)	7.8 (9)	11.3 (12)	15.0 (15)
Major bleeding	17.9(21/117)	21.4 (25)	23.3 (27)	23.3 (27)	23.3 (27)	23.3 (27)
MI – Peri-procedural (≤72 h)	3.4 (4/117)	3.3 (4)	3.3 (4)	3.3 (4)	3.3 (4)	3.3 (4)
MI – Spontaneous (>72 h)	0.0 (0/117)	0.0 (0)	0.0 (0)	1.1 (1)	1.1 (1)	2.4 (2)
AKI Stage 2	1.7 (2/115)	1.7 (2)	1.7 (2)	3.4 (4)	1.7 (2)	1.7 (2)
AKI Stage 3	1.7 (2/115)	1.7 (2)	1.7 (2)	1.7 (2)	1.7 (2)	1.7 (2)
Repeat procedure[b]	0.0 (0/115)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
Hospitalization[c]	4.3 (5/115)	5.2 (6)	8.0 (9)	12.2 (13)	17.5 (18)	19.8 (20)
Atrial fibrillation – New onset	5.2 (6/115)	6.0 (7)	6.0 (7)	6.0 (7)	6.0 (7)	6.0 (7)
Atrial flutter – New onset	0.0 (0/115)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
Coronary obstruction[d]	0.9 (1/115)	0.8 (1)	0.8 (1)	0.8 (1)	0.8 (1)	0.8 (1)
Ventricular septal perforation[d]	0.0 (0/115)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
Mitral apparatus damage[d]	2.6 (3/115)	2.6 (3)	2.6 (3)	2.6 (3)	2.6 (3)	2.6 (3)
Cardiac tamponade[d]	4.3 (5/117)	4.2 (5)	4.2 (5)	4.2 (5)	4.2 (5)	4.2 (5)

Table 4.1-4: Clinical and Echocardiographic Outcomes to 5 Years – REPRISE II Main Cohort (N=120)

Outcomes	30 Days	1 Year	2 Years	3 Years	4 Years	5 Years
Prosthetic valve malapposition[e]	0.0 (0/115)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
Prosthetic valve thrombosis	0.0 (0/115)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
Prosthetic valve endocarditis	0.0 (0/115)	0.9 (1)	2.8 (3)	2.8 (3)	2.8 (3)	2.8 (3)
Aortic Valve Performance by Transthoracic Echocardiography (Core Lab Assessment)						
EOA (cm^2)[f]	1.67±0.43 (78)	1.65±0.51 (79)	1.66±0.45 (69)	1.62±0.48 (57)	1.55±0.43 (55)	1.60±0.48 (40)
Mean gradient (mmHg)[g]	11.45±5.20 (97)	12.58±5.66 (92)	12.30±6.18 (75)	11.26±5.23 (61)	12.41±6.88 (55)	14.43±6.44 (43)
Peak aortic gradient (mmHg)[h]	21.30±9.26 (97)	23.09±10.14 (92)	21.25±11.03 (75)	21.27±9.65 (61)	22.20±11.03 (55)	26.55±11.34 (43)
Peak aortic velocity (m/s)[i]	2.25±0.48 (97)	2.35±0.50 (92)	2.23±0.56 (75)	2.25±0.51 (61)	2.29±0.54 (55)	2.52±.53 (43)
Paravalvular Aortic Regurgitation						
None	78.1 (75/96)	86.4 (76/88)	87.8 (65/74)	87.5 (49/56)	74.1 (43/58)	59.1 (26/44)
Trace/trivial	5.2 (5/96)	2.3 (2/88)	2.7 (2/74)	0.0 (0/56)	10.3 (6/58)	20.5 (9/44)
Mild	15.6 (15/96)	11.4 (10/88)	9.5 (7/74)	12.5 (7/56)	13.8 (8/58)	15.9 (7/44)
Moderate	1.0 (1/96)	0.0 (0/88)	0.0 (0/74)	0.0 (0/56)	1.7 (1/58)	4.5 (2/44)
Severe	0.0 (0/96)	0.0 (0/88)	0.0 (0/74)	0.0 (0/56)	0.0 (0/58)	0.0 (0/44)

Values are presented as % (count/sample size), % (n), or mean±SD (n); for clinical events, binary rates are presented through 30 days, time-to-event (Kaplan-Meier) data are presented at 1 year and beyond.

a: Due to new conduction disturbances or arrhythmias

b: For valve-related dysfunction (surgical or interventional)

c: For valve-related symptoms or worsening congestive heart failure (NYHA class III or IV)

d: Peri-procedural

e: Including valve migration, valve embolization, ectopic valve deployment, or TAV-in-TAV

f: Baseline effective orifice area (cm^2): 0.68 ± 0.19 (11); change from baseline is significant at all time points

g: Baseline mean aortic gradient (mmHg): 53.9±20.9 (11); change from baseline is significant at all time points

h: Baseline peak aortic gradient (mmHg): 76.54±23.56 (104); change from baseline is significant at all time points

i: Baseline peak aortic velocity (m/s): 4.30±0.67 (105); change from baseline is significant at all time points

Abbreviation: AKI=acute kidney injury; EOA=effective orifice area; MI=myocardial infarction; PPM=permanent pacemaker; TAV=transcatheter aortic valve; VARC=Valve Academic Research Consortium

References: Meredith 2014[66], 2015[67], 2016[68,69]; Hildick-Smith 2017[70]; Dumonteil 2018[71]

The REPRISE II study was subsequently expanded to enroll 130 additional subjects in the REPRISE II extended trial cohort at centers in Australia and Europe. The main trial cohort and the extended trial cohort had the same overall study design. The main trial cohort received additional neurologic evaluation and annual imaging assessments to determine valve frame integrity. Per the protocol, a statistically powered analysis based on the combined main and extended trial cohorts (full cohort, N=250) was performed for the primary safety endpoint (mortality at 30 days). The primary safety endpoint was analyzed on an ITT basis. A one-sample *z* test was used to test the one-sided hypothesis that 30-day all-cause mortality is less than the prespecified PG of 16% (based on an expected rate of 9.8% plus a testing

margin of 6.2%). All-cause mortality at 30 days was 4.4% with an upper confidence bound of 6.97% and the primary safety endpoint was met[72].

Table 4.1-5 shows device performance endpoints, clinical outcomes, and echocardiographic outcomes through 4 years for the full cohort. Outcomes were similar to that reported for the main cohort (see **Table 4.1-3**). At 30 days, the mean aortic valve gradient was 11.70±6.77 mmHg, mortality was 4.4%, and the disabling stroke rate was 3.3%. Through 1 year, mortality was 12% and the disabling stroke rate was 3.6%; valve endocarditis (N=2) and thrombosis (N=3) were successfully resolved with antibiotics and anticoagulant therapy, respectively, without sequelae. The new PPM implant rate was 29.6% at 30 days. Reported rates for early conduction abnormalities and the need for PPM implantation after TAVR have ranged from 3% to 8% with SAPIEN and 14% to 40% with CoreValve[73]. Mechanical pressure from the valve frame may cause conduction tissue injury or inflammation during TAVR, especially with longer stent frames, self-expanding valves, pre- or post-dilatation and deep implant depth[74]. With an expanded length compared to previous generation balloon-expandable valves, the SAPIEN 3 valve has also been associated with somewhat higher rates of PPM[75,76]. While undesirable, PPM early after TAVR has generally not been associated with an increase in mortality[77-79], although recent reports from the PARTNER trial and registries did find patients with prior pacemaker, new PPM, or chronic left bundle branch block had attenuated improvement in left ventricular ejection fraction (LVEF), more repeat hospitalization, and higher rates of all-cause death at 1 year compared to patients who had none of these conditions[80,81]. However, PPM was associated with significantly less unexpected death in another study[82].

There was no severe PVR and none/trace/trivial PVR in 85% of REPRISE II full-cohort subjects at 30 days. A number of independent studies[55,56,83-90] and large meta-analyses[57,91] have found an association between PVR post TAVR and early or late mortality; moderate/severe PVR, often more common with CoreValve than SAPIEN[55,87,88], has been an independent predictor of both. A recent meta-analysis suggested that mild PVR may also be associated with increased all-cause and cardiovascular mortality[59]. The low PVR rate observed at 30 days with Lotus was maintained at 1 year and 4 years as most subjects (91% and 88%, respectively) had none/trace/trivial PVR, 2 subjects had moderate PVR at 4 years, and there was no severe PVR.

In summary, the observed clinical results in the full cohort are consistent with other TAVR studies and the PVR rates are lower. The results of the REPRISE II study support the safety and performance of the Lotus Valve System.

Table 4.1-5: Clinical and Echocardiographic Outcomes to 4 Years – REPRISE II Full Cohort (N=250)

Outcomes	30 Days	1 Year	2 Years	3 Years	4 Years
Clinical Outcomes (CEC Adjudicated, VARC Definitions)					
All-cause mortality	4.4 (11/249)	11.8 (29)	19.1 (47)	28.3 (69)	38.7 (94)
Cardiovascular	4.0 (10/249)	7.8 (19)	9.5 (23)	14.3 (33)	19.0 (42)
Stroke	7.1 (17/241)	8.6 (21)	9.6 (23)	10.6 (25)	10.6 (25)
Disabling stroke	3.3 (8/241)	3.7 (9)	4.7 (11)	6.2 (14)	6.2 (14)

Table 4.1-5: Clinical and Echocardiographic Outcomes to 4 Years – REPRISE II Full Cohort (N=250)

Outcomes	30 Days	1 Year	2 Years	3 Years	4 Years
Major vascular complications	5.4 (13/241)	5.2 (13)	5.2 (13)	5.2 (13)	5.2 (13)
New PPM[a]	29.6 (72/243)	33.1 (81)	35.1 (85)	35.7 (86)	36.3 (87)
Life-threatening/disabling bleeding	7.3 (18/247)	9.4 (23)	10.7 (26)	10.7 (26)	14.4 (32)
Major bleeding	21.5 (53/247)	23.7 (58)	25.1 (61)	25.7 (62)	25.7 (62)
MI – Peri-procedural (≤72 h)	2.9 (7/243)	2.8 (7)	2.8 (7)	2.8 (7)	2.8 (7)
MI – Spontaneous (>72 h)	0.0 (0/243)	0.0 (0)	0.0 (0)	1.6 (3)	2.2 (4)
AKI Stage 2	1.3 (3/240)	1.2 (3)	1.2 (3)	1.2 (3)	1.2 (3)
AKI Stage 3	1.7 (4/240)	1.6 (4)	1.6 (4)	1.6 (4)	1.6 (4)
Repeat procedure[b]	0.0 (0/240)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
Hospitalization[c]	2.9 (7/240)	7.1 (17)	9.9 (23)	14.1 (31)	19.7 (41)
Atrial fibrillation – New onset	5.8 (14/241)	6.6 (16)	6.6 (16)	6.6 (16)	6.6 (16)
Atrial flutter – New onset	0.8 (2/241)	0.4 (1)	0.4 (1)	0.4 (1)	0.4 (1)
Coronary obstruction[d]	0.8 (2/241)	0.8 (2)	0.8 (2)	0.8 (2)	0.8 (2)
Ventricular septal perforation[d]	0.0 (0/240)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
Mitral apparatus damage[d]	1.7 (4/240)	1.6 (4)	1.6 (4)	1.6 (4)	1.6 (4)
Cardiac tamponade[d]	3.7 (9/246)	3.2 (8)	3.2 (8)	3.2 (8)	3.2 (8)
Prosthetic valve malapposition[e]	0.0 (0/240)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
Prosthetic valve thrombosis	0.0 (0/240)	1.3 (3)	1.3 (3)	1.8 (4)	2.4 (5)
Prosthetic valve endocarditis	0.0 (0/240)	0.9 (2)	1.8 (4)	1.8 (4)	1.8 (4)
Aortic Valve Performance by Transthoracic Echocardiography (Core Lab Assessment)					
EOA (cm^2)[f]	1.74±0.45 (149)	1.68±0.49 (157)	1.64±0.47 (123)	1.55±0.47 (119)	1.50±0.43 (95)
Mean gradient (mmHg)[g]	11.70±6.77 (183)	12.49±5.35 (176)	12.18±5.99 (135)	12.19±6.02 (125)	12.69±7.13 (97)
Peak aortic gradient (mmHg)[h]	20.75 ± 9.05 (183)	21.90±9.40 (176)	21.25±10.15 (135)	22.32±10.38 (125)	23.11±12.14 (97)
Peak aortic velocity (m/s)[i]	2.23 ± 0.47 (183)	2.29 ± 0.47 (176)	2.24±0.53 (135)	2.30±0.53 (125)	2.33±0.56 (97)
Paravalvular Aortic Regurgitation					
None	80.2 (142/177)	82.2 (134/163)	87.1 (115/132)	77.5 (100/129)	73.7 (73/99)
Trace/trivial	5.6 (10/177)	3.1 (5/163)	3.0 (4/132)	10.1 (13/129)	14.1 (14/99)
Mild	13.6 (24/177)	14.7 (24/163)	9.8 (13/132)	10.9 (14/129)	10.1 (10/99)
Moderate	0.6 (1/177)	0.0 (0/163)	0.0 (0/132)	1.6 (2/129)	2.0 (2/99)
Severe	0.0 (0/177)	0.0 (0/163)	0.0 (0/132)	0.0 (0/129)	0.0 (0/99)

Values are presented as % (count/sample size), % (n), or mean±SD (n); for clinical events, binary rates are presented through 30 days, time-to-event (Kaplan-Meier) data are presented at 1 year and beyond.

a: Due to new conduction disturbances or arrhythmias

b: For valve-related dysfunction (surgical or interventional)

c: For valve-related symptoms or worsening congestive heart failure (NYHA class III or IV)

d: Peri-procedural

e: Including valve migration, valve embolization, ectopic valve deployment, or TAV-in-TAV

f: Baseline effective orifice area (cm2): 0.68 ± 0.19 (201); change from baseline is significant at all time points

g: Baseline mean aortic gradient (mmHg): 45.36±13.75 (216); change from baseline is significant at all time points

h: Baseline peak aortic gradient (mmHg): 78.41±21.21 (216); change from baseline is significant at all time points

Table 4.1-5: Clinical and Echocardiographic Outcomes to 4 Years – REPRISE II Full Cohort (N=250)

Outcomes	30 Days	1 Year	2 Years	3 Years	4 Years

i: Baseline peak aortic velocity (m/s): 4.270±0.60 (217); change from baseline is significant at all time points
Abbreviation: AKI=acute kidney injury; EOA=effective orifice area; MI=myocardial infarction; PPM=permanent pacemaker; TAV=transcatheter aortic valve; VARC=Valve Academic Research Consortium
References: Meredith 2016[92], 2017[93]; Tchétché 2017[94]; Blackman 2018[95]

4.1.2.3. RESPOND Post-Market Surveillance Study

The Repositionable Lotus Valve System – Post-market Evaluation of Real World Clinical Outcomes (RESPOND; NCT02031302) study is a prospective, open label, single-arm, multicenter, observational post-market surveillance study designed to collect real-world clinical and device performance outcomes data with the Lotus Valve System as used in routine clinical practice to treat subjects with severe calcific aortic stenosis. There were 1014 consecutive (defined as a commitment by the participating investigators at each study center to enroll all consented subjects admitted for TAVR who are selected to receive a Lotus Valve) subjects enrolled at 41 study centers in Europe, New Zealand, Israel, and Colombia. Independent data assessments include core laboratory review of baseline, pre-discharge, and 1-year echocardiography data and adjudication of center-reported mortality and stroke events by an independent medical reviewer (IMR). The statistically powered primary endpoint of 30-day mortality was compared to a predefined performance goal. Clinical follow-up will extend through 5 years. Data through 30-day and 1-year follow-up are provided below.

Procedural device success among the as-treated analysis set is shown in **Table 4.1-6**. Correct positioning of one transcatheter valve in the proper location was achieved in 99.7% of subjects. There was no moderate or severe prosthetic valve regurgitation (central or paravalvular) in 99.6% of subjects.

Table 4.1-6: Procedural Device Success, RESPOND As-Treated Analysis Set

Variable	N=996
Procedural mortality	0.2% (2/996)
Correct positioning of a single transcatheter valve into the proper anatomical location	99.7% (993/996)
Mean aortic valve gradient <20 mmHg	96.4% (894/927)
Peak velocity <3m/sec	96.1% (891/927)
No moderate or severe prosthetic valve regurgitation[a]	99.6% (931/935)

Numbers are % (count/sample size).
a: Total prosthetic aortic valve regurgitation (includes central and paravalvular) per VARC 2[62] definition; core-lab adjudicated
Abbreviation: VARC=Valve Academic Research Consortium
Reference: Falk 2017[96]

The 30-day primary endpoint, all-cause mortality in the ITT population, was 2.6% (26/1005) with a one-sided upper confidence bound of 4.1%[96]. This was significantly below (P<0.0001) the performance goal of 14.0% and the 30-day primary endpoint was met. The statistically

powered secondary effectiveness endpoint, rate of moderate or severe PVR pre-discharge (as measured by TTE and assessed by an independent core laboratory) in the as-treated analysis set was 0.3% (3/934) with a one-sided upper bound of 1.1%. This was significantly below (P<0.0001) the performance goal of 16.5% and the powered secondary effectiveness endpoint was met.

Table 4.1-7 shows secondary safety endpoint outcomes assessed at 30 days and 1 year in the RESPOND as-treated analysis set. At 30 days, all-cause mortality was 2.2%, in-hospital mortality was 1.8%, and disabling stroke was 2.3%. Mortality was 11.7% and disabling stroke was 4.0% at 1 year. **Table 4.1-8** shows core laboratory TTE assessments pre-discharge and at 1 year in the as-treated analysis set. Mean aortic gradient improved significantly (P<0.0001) from 38.0±15.5 mmHg at baseline to 10.8±4.6 mmHg at discharge and remained low at 1 year (10.8±5.1 mmHg, P<0.0001). There was also a significant (P<0.0001) improvement in mean effective orifice area (EOA) from 0.7±0.2 cm^2 at baseline to 1.8±0.5 cm^2 at discharge, which was sustained at 1 year (1.8±0.4 cm^2, P<0.0001). There were no cases of severe PVR at discharge or 1 year. There were 3 cases of moderate PVR at discharge and 2 cases (0.4%) at 1 year; in >90% of evaluable subjects PVR was trivial or absent.

Table 4.1-7: RESPOND Secondary Endpoints – VARC Safety Assessments at 30 Days and 1 Year Post-Procedure; As-Treated Analysis Set

Outcome	30 Days	1 Year
IMR-Adjudicated Events		
All-cause mortality and disabling stroke	4.1% (41/996)	13.7% (135/988)
All-cause mortality	2.2% (22/996)	11.7%(116/988)
In-hospital mortality	1.8% (18/996)	1.8% (18/996)
Cardiovascular	2.0% (20/996)	7.5% (74/988)
Non-cardiovascular	0.2% (2/996)	4.3% (42/988)
Disabling stroke	2.3% (23/996)	4.0% (4/998)
Center-Reported Events		
Major vascular complications	3.0% (30/996)	3.3% (33/988)
Life-threatening or disabling bleeding	2.2% (22/996)	3.5% (35/988)
Acute kidney injury (Stage 2 or 3, including renal replacement therapy)	1.6% (16/996)	1.7% (17/988)
New conduction disturbances and need for permanent pacemaker implantation	30.0% (299/996)	32.0% (316/988)
Peri-procedural MI (≤72 hours)	0.4% (4/996)	0.4% (4/988)
Spontaneous MI (>72 hours after index procedure)	0.3% (3/996)	1.3% (13/988)
Valve-related dysfunction requiring repeat procedure (surgical/interventional)	0.1% (1/996)	0.2% (2/988)
Hospitalization for valve-related symptoms or worsening congestive heart failure	1.4% (14/996)	7.5% (74/988)
Prosthetic aortic valve thrombosis	0.4% (4/996)	0.8% (8/988)
Prosthetic aortic valve endocarditis	0.2% (2/996)	1.3% (13/988)

Table 4.1-7: RESPOND Secondary Endpoints – VARC Safety Assessments at 30 Days and 1 Year Post-Procedure; As-Treated Analysis Set

Outcome	30 Days	1 Year

Numbers are % (count/sample size).
Abbreviations: IMR=Independent Medical Reviewer; MI=myocardial infarction; VARC=Valve Academic Research Consortium
References: Falk 2017[96]; Van Mieghem 2017[97]

Table 4.1-8: Core Laboratory Echocardiographic Assessments at Pre-Discharge and 1 Year, RESPOND As-Treated Analysis Set

Parameter	Pre-Discharge	1 Year
Aortic valve area (effective orifice area) (cm^2)[a]	1.8±0.5 (854)	1.8±0.4 (516)
Mean aortic valve gradient (mmHg)[b]	10.8±4.6 (927)	10.8±5.1 (542)
Peak aortic gradient (mmHg)	19.3±8.0 (927)	19.1±8.8 (542)
Peak aortic velocity (m/s)	2.2±0.4 (927)	2.1±0.5 (542)
Paravalvular Aortic Regurgitation		
None	80.8% (755/934)	83.9% (457/545)
Trace/trivial	11.1% (104/934)	10.6% (58/545)
Mild	7.7% (72/934)	5.1% (28/545)
Moderate	0.3% (3/934)	0.4% (2/545)
Severe	0.0% (0/934)	0.0% (0/545)

Numbers are mean±SD or % (count/sample size).
a: Baseline effective orifice area (cm^2): 0.7 ± 0.2 (877)
b: Baseline mean aortic gradient (mmHg): 38.0 ± 15.5 (923)
References: Falk 2017[96]; Van Mieghem 2017[97]

Compared to tricuspid aortic valves, bicuspid aortic valves have a larger annulus perimeter, asymmetrical valve orifice, and heavily calcified leaflets/raphe[98,99]. Thus, TAVR in bicuspid aortic valves may be subject to an increased risk of complications related to irregular and incomplete expansion of the prosthetic valve[100]. Existing data with first generation TAVR valves indicate a higher post-TAVR rate of moderate/severe PVR among patients with bicuspid aortic valves (25%) compared with tricuspid aortic valves (15%; P=0.05)[101]. In RESPOND, 31 patients (3.1%) were identified as having a bicuspid aortic valve[102]; 81.5% were classified as Sievers Type 1[103], 14.8% as Sievers Type 0, and 3.7% as Sievers Type 2. Subjects with bicuspid valves were older and at baseline had a lower mean effective orifice area (0.6 cm^2 vs. 0.7 cm^2, P=0.0043) and a higher mean aortic valve gradient (51.6 mmHg vs. 43.6 mmHg, P=0.0132). **Table 4.1-9** compares echocardiographic outcomes at pre-discharge and clinical outcomes at 30 days in the 2 groups. Mean effective orifice area increased and mean aortic valve gradient decreased from baseline to discharge in both groups. Notably, there were no significant differences between groups in echocardiographic or clinical outcome measures after TAVR. Although this substudy is limited by the small

number of RESPOND patients with bicuspid anatomy, the observed results support the safety and effectiveness of TAVR with the Lotus Valve in bicuspid aortic valve stenosis.

Table 4.1-9: Bicuspid and Non-Bicuspid Groups in RESPOND – As-Treated Analysis Set (N=996)

Outcome	Bicuspid (N=31)	Non-Bicuspid (N=965)	*P* value
30-Day Principal Safety Results (VARC Definitions)			
All-cause mortality	3.2% (1/31)	2.2% (21/955)	0.51
Cardiovascular	3.2% (1/31)	2.0% (19/955)	0.48
Disabling stroke	3.2% (1/31)	2.2% (21/955)	0.51
Non-disabling stroke	0.0% (0/31)	0.8% (8/955)	1.00
Major vascular complications	6.5% (2/31)	2.8% (27/955)	0.23
New conduction disturbances and need for permanent pacemaker implantation	19.4% (6/31)	30.4% (290/955)	0.19
Life-threatening or disabling bleeding	6.5% (2/31)	2.1% (20/955)	0.15
Acute kidney injury	3.2% (1/31)	2.5% (24/955)	0.56
Myocardial infarction	0.0% (0/31)	0.6% (6/955)	1.00
Valve Performance by TTE (Pre-Discharge – Core Lab Assessment)			
Mean effective orifice area (cm^2)[a]	1.7±0.43 (28)	1.8±0.45 (826)	0.20
Mean aortic valve gradient (mmHg)[b]	11.8±5.06 (29)	10.8±4.53 (898)	0.21
Paravalvular Aortic Regurgitation			
None	69.0% (20/29)	81.2% (735/905)	0.10
Trace/Trivial	17.2% (5/29)	10.9% (99/905)	0.36
Mild	13.8% (4/29)	7.5% (68/905)	0.27
Moderate	0.0% (0/29)	0.3% (3/905)	1.00
Severe	0.0% (0/29)	0.0% (0/905)	–

Numbers are % (count/sample size) or mean±SD (n).

a: Baseline effective orifice area (cm^2) was significantly different between the 2 groups: 0.6±0.2 (28) vs. 0.7±0.2 (847), *P*=0.004

b: Baseline mean aortic gradient (mmHg) was significantly different between the 2 groups: 51.6±16.97 (30) vs. 43.6±17.44 (876), *P*=0.013

Abbreviations: TTE=transthoracic echocardiography; VARC=Valve Academic Research Consortium
Reference: Blackman 2016[102]

After enrollment of the main RESPOND cohort was completed the study was extended to enroll an additional cohort (RESPOND Extension) to assess center-driven implantation technique with the commercially available Lotus Valve System with Depthguard™ technology. Depthguard results in a slightly decreased rate of retraction of the outer sheath during valve deployment. This minimizes interaction between the frame and the LVOT during deployment and could limit the need for PPM implantation.

Table 4.1-10 shows clinical outcomes at 30 days and echocardiographic outcomes at pre-discharge. Mortality and disabling stroke were 0.0% and 2.0%, respectively, and new PPM implantation was 18.0%. There were no cases of moderate or severe PVR; in 86% of cases PVR was trivial or absent.

Table 4.1-10: RESPOND Extension – VARC Safety Assessments (30 Days) and Core Lab Echocardiographic Assessments (Pre-Discharge); As-Treated Analysis Set

Outcome	N=50
IMR-Adjudicated Events (30 Days)	
All-cause mortality and disabling stroke	2.0% (1/50)
All-cause mortality	0.0% (0/50)
Disabling stroke	2.0% (1/50)
Center-Reported Events (30 Days)	
Major vascular complications	2.0% (1/50)
Life-threatening or disabling bleeding	0.0% (0/50)
Acute kidney injury (Stage 2 or 3, including renal replacement therapy)	2.0% (1/50)
New conduction disturbances and need for permanent pacemaker implantation	18.0% (9/50)
Peri-procedural MI (≤72 hours)	0.0% (0/50)
Spontaneous MI (>72 hours after index procedure)	0.0% (0/50)
Valve-related dysfunction requiring repeat procedure (surgical/interventional)	0.0% (0/50)
Hospitalization for valve-related symptoms or worsening congestive heart failure	0.0% (0/50)
Prosthetic aortic valve thrombosis	0.0% (0/50)
Prosthetic aortic valve endocarditis	0.0% (0/50)
Echocardiography (Pre-Discharge)	
Aortic valve area (effective orifice area) (cm^2)[a]	1.7±0.3 (35)
Mean aortic valve gradient (mmHg)[b]	11.8±4.4 (37)
Peak aortic gradient (mmHg)	21.1±8.5 (37)
Peak aortic velocity (m/s)	2.3±0.4 (37)
Paravalvular Aortic Regurgitation	
None	64.9% (24/37)
Trace/trivial	21.6% (8/37)
Mild	13.5% (5/37)
Moderate	0.0% (0/37)
Severe	0.0% (0/37)

Numbers are mean±SD or % (count/sample size).
a: Baseline effective orifice area (cm^2): 0.7 ± 0.2 (44)
b: Baseline mean aortic gradient (mmHg): 39.8 ± 13.7 (45)
Abbreviations: IMR=Independent Medical Reviewer; MI=myocardial infarction; VARC=Valve Academic Research Consortium
Reference: Van Mieghem 2017[104]

In summary, the observed 30-day and 1-year outcomes among RESPOND subjects and 30-day outcomes in RESPOND Extension show good hemodynamic results, a very low PVR rate, low mortality, and overall favorable event rates. There also were no significant differences in pre-discharge echocardiographic or 30-day clinical outcome measures between subjects with and without a native bicuspid valve. The results from this study have demonstrated that the commercially available Lotus Valve System is a safe and effective treatment for subjects with severe calcific aortic stenosis in routine clinical practice.

4.1.2.4. REPRISE III Randomized Controlled Trial

The REPRISE III pivotal study (REpositionable Percutaneous Replacement of Stenotic Aortic Valve through Implantation of Lotus™ Valve System – Randomized Clinical Evaluation; NCT02202434) includes a prospective, multicenter, randomized, controlled trial (RCT) designed to evaluate the safety and effectiveness of the Lotus™ Valve System (23mm, 25mm, or 27mm valve; test device) compared to a commercially available self-expanding transcatheter heart valve (CoreValve® device, Medtronic Corp, Dublin, Ireland; 26mm, 29mm, and 31mm valve; control device) in symptomatic subjects with severe calcific aortic stenosis who are considered extreme or high risk for surgical valve replacement. There were 912 subjects randomized at 55 centers in the United States, Germany, France, Australia, The Netherlands, and Canada. Subjects were considered enrolled in the study upon randomization. Clinical follow-up will extend through 5 years. The trial included independent core laboratory analysis and independent event adjudication with data validated by independent statisticians.

The 30-day primary safety composite endpoint for REPRISE III includes all-cause mortality, stroke, life-threatening and major bleeding events, stage 2 or 3 acute kidney injury, and major vascular complications. The primary effectiveness endpoint for noninferiority includes the combined rate of mortality, disabling stroke, and moderate/severe PVR at 1 year post implant procedure. Other measurements incorporated the minimum data collection and endpoints recommended and defined by the VARC guidelines. Subject screening, data collection, and event assessments were as described for REPRISE II (Section **4.1.2.2**) Data for the primary endpoint in the RCT have been published[44].

A total of 607 subjects were randomized to the Lotus group and 305 were randomized to the CoreValve group (ITT analysis set). Subject analysis groups are shown in **Figure 4.1-1**. The first-generation Lotus Valve System was used throughout the study while the second-generation CoreValve Evolut R device was introduced mid-way in the study. Thus, in the implanted analysis set of the CoreValve treatment group 51.5% of subjects received CoreValve and 48.5% received CoreValve Evolut R (153/297 and 144/297, respectively).

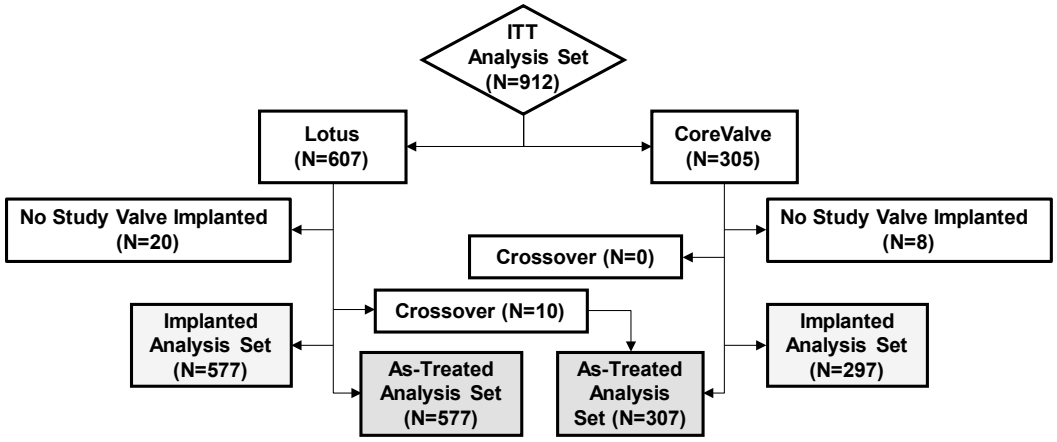


Figure 4.1-1: REPRISE III Randomized Subject Analysis Groups

The ITT population includes all randomized subjects, whether or not an assigned study device was implanted. The implanted population includes ITT subjects who received the assigned, randomized study device. The as-treated population includes ITT subjects who received a study device, based on treatment actually received.

The REPRISE III primary safety endpoint was met because in the implanted analysis set the rate for the Lotus group (20.3%) was non-inferior to the rate for the CoreValve group (17.2%). Non-inferiority was concluded because the one-sided upper 97.5% confidence bound on the difference between treatment groups (Lotus minus CoreValve; 3.1%) was less than the non-inferiority margin of 10.5% with a *P* value <0.025 (*P*=0.0027). Non-inferiority was also shown for the ITT and as-treated analysis sets.

The primary effectiveness endpoint was met because in the implanted analysis set the rate for Lotus group (15.4%) was non-inferior to the rate for CoreValve (25.5%). Non-inferiority was concluded because the one-sided upper 97.5% confidence bound on the difference between treatment groups (Lotus minus CoreValve; -4.41%) was less than the non-inferiority margin of 9.5% with a *P* value <0.025 (*P*<0.0001). Non-inferiority was also shown for the ITT and as-treated analysis sets. The rate of the primary effectiveness endpoint for Lotus was shown to be superior to that for CoreValve in the ITT analysis set (*P*=0.0006) and also in the implanted and as-treated analysis sets.

Table 4.1-11 shows clinical and echocardiographic outcomes at 30 days and 1 year. The following were similar between the 2 cohorts:

- All-cause mortality in the CoreValve arm and Lotus arm was 2.3% and 2.5%, respectively (*P*=0.86), at 30 days and 13.5% and 11.9%, respectively (*P*=0.51), at 1 year.
- Cardiovascular mortality was 2.3% (CoreValve) and 2.3% (Lotus, *P*=0.99) at 30 days and 9.8% (CoreValve) and 7.7% (Lotus, *P*=0.29) at 1 year.
- The overall stroke rate in the CoreValve and Lotus cohorts was 4.3% and 4.8%, respectively (*P*=0.72), at 30 days and 9.4% and 7.0%, respectively (*P*=0.20), at 1 year.

- The rate of major vascular complications was 5.3% (CoreValve) and 7.0% (Lotus, *P*=0.32) at 30 days and 6.1% (CoreValve) and 7.7% (Lotus, *P*=0.38) at 1 year.
- Life-threatening/disabling bleeding was 5.0% (CoreValve) and 8.0% (Lotus, *P*=0.09) at 30 days and 9.8% (CoreValve) and 9.9% (Lotus, *P*=0.96) at 1 year.

The following were statistically significantly different between the 2 cohorts:

- The disabling stroke rate in the CoreValve and Lotus cohorts was 3.3% and 2.0%, respectively (*P*=0.23), at 30 days and 7.1% and 3.6%, respectively (*P*=0.02), at 1 year.
- The rate of permanent pacemaker implantation among subjects without a prior pacemaker was 19.6% (CoreValve) and 35.5% (Lotus, *P* <0.001) at 30 days and 23.0% (CoreValve) and 41.4% (Lotus, *P* <0.001) at 1 year.
- The valve thrombosis rate was 0.0% for both cohorts at 30 days; it was 0.0% (CoreValve) and 1.5% (Lotus, *P*=0.03) at 1 year.
- Repeat procedures for prosthetic valve-related dysfunction occurred in 1.0% of CoreValve subjects and 0.0% of Lotus subjects at 30 days (*P*=0.04) and 2.0% (CoreValve) and 0.2% (Lotus) by1 year (*P*=0.007).
- Prosthetic valve malpositioning (including valve migration, valve embolization, and ectopic valve deployment to discharge/7 days) occurred in 2.6% of subjects in the CoreValve group and 0.0% of subjects in the Lotus group (*P*<0.001).
- TAV-in-TAV deployment occurred in 3.0% of subjects in the CoreValve group and in no subjects in the Lotus group (*P* <0.001).
- Mean gradient was significantly lower and EOA was significantly higher in the CoreValve group at discharge and beyond (both *P* <0.001).

There was significantly less PVR with Lotus compared to CoreValve at all time points (*P*<0.001).

Table 4.1-11: Clinical and Echocardiographic Outcomes at 30 Days and 1 Year in REPRISE III RCT

Measure	30 Days[a]			1-Year[a]		
	CoreValve (N=305)	Lotus (N=607)	*P* Value	CoreValve (N=305)	Lotus (N=607)	*P* Value
Clinical Outcomes (CEC Adjudicated, VARC Definitions)						
All-cause mortality	2.3% (7/303)	2.5% (15/601)	0.86	13.5% (40/297)	11.9% (70/587)	0.51
Cardiovascular	2.3% (7/303)	2.3% (14/601)	0.99	9.8% (29/297)	7.7% (45/587)	0.29
Stroke	4.3% (13/303)	4.8% (29/601)	0.72	9.4% (28/297)	7.0% (41/587)	0.20
Disabling stroke	3.3% (10/303)	2.0% (12/601)	0.23	7.1% (21/297)	3.6% (21/587)	0.02
All-cause mortality or disabling stroke	5.3% (16/303)	4.0% (24/601)	0.37	17.8% (53/297)	13.3% (78/587)	0.07
Major vascular complications	5.3% (16/303)	7.0% (42/601)	0.32	6.1% (18/297)	7.7% (45/587)	0.38
Access site related	3.3% (10/303)	4.7% (28/601)	0.34	3.7% (11/297)	5.1% (30/587)	0.35
New PPM[b]	15.8% (48/303)	29.1% (175/601)	<0.001	18.5% (55/297)	34.2% (201/587)	<0.001
No prior PPM[b]	19.6% (48/245)	35.5% (175/493)	<0.001	23.0% (55/239)	41.4% (201/485)	<0.001
Life-threatening/disabling bleeding	5.0% (15/303)	8.0% (48/601)	0.09	9.8% (29/297)	9.9% (58/587)	0.96
MI ≤ 72 hours	1.0% (3/303)	0.5% (3/601)	0.41	1.3% (4/297)	0.5% (3/587)	0.23
MI > 72 hours	0.3% (1/303)	0.2% (1/601)	1.00	3.4% (10/297)	2.7% (16/587)	0.59
AKI – Stage 2/3	3.6% (11/303)	2.5% (15/601)	0.34	3.7% (11/297)	2.6% (15/587)	0.34
Repeat procedure[c]	1.0% (3/303)	0.0% (0/601)	0.04	2.0% (6/297)	0.2% (1/587)	0.007
Hospitalization[d]	3.0% (9/303)	1.7% (10/601)	0.20	13.8% (41/297)	11.2% (66/587)	0.27
New onset atrial fibrillation/flutter	4.3% (13/303)	5.8% (35/601)	0.33	4.7% (14/297)	6.6% (39/587)	0.25
Coronary obstruction[e]	0.7% (2/303)	0.2% (1/601)	0.26	0.7% (2/297)	0.2% (1/587)	0.26
Ventricular septal perforation[e]	0.0% (0/303)	0.2% (1/601)	1.00	0.0% (0/297)	0.2% (1/587)	1.00
Mitral apparatus damage[e]	0.3% (1/303)	0.0% (0/601)	0.34	0.3% (1/297)	0.0% (0/587)	0.34
Cardiac tamponade[e]	1.0% (3/303)	2.5% (15/601)	0.13	1.3% (4/297)	2.6% (15/587)	0.24
Prosthetic aortic valve malapposition[f]	2.6% (8/303)	0.0% (0/601)	<0.001	2.7% (8/297)	0.0% (0/587)	<0.001
TAV-in-TAV deployment	3.0% (9/303)	0.0% (0/601)	<0.001	3.7% (11/297)	0.0% (0/587)	<0.001
Prosthetic aortic valve thrombosis	0.0% (0/303)	0.0% (0/601)	Undefined	0.0% (0/297)	1.5% (9/587)	0.03

Table 4.1-11: Clinical and Echocardiographic Outcomes at 30 Days and 1 Year in REPRISE III RCT

Measure	30 Days[a]			1-Year[a]		
	CoreValve (N=305)	Lotus (N=607)	*P* Value	CoreValve (N=305)	Lotus (N=607)	*P* Value
Prosthetic aortic valve endocarditis	0.0% (0/303)	0.2% (1/601)	1.00	0.0% (0/297)	0.7% (4/587)	0.31
Valve Performance by TTE (Core Lab Assessment)						
EOA (cm^2)[g]	1.98±0.51 (238)	1.59±0.45 (506)	<0.001	1.69±0.52 (199)	1.49±0.45 (420)	<0.001
Mean aortic valve gradient (mmHg)[h]	7.25±3.44 (261)	12.00±6.08 (544)	<0.001	7.89±3.48 (219)	12.29±5.83 (462)	<0.001
Peak aortic gradient (mmHg)	13.59±6.21 (261)	21.46±10.27 (545)	<0.001	15.22±6.44 (219)	22.74±10.53 (462)	<0.001
Peak aortic velocity (m/s)	1.80±0.40 (261)	2.26±0.46 (545)	<0.001	1.91±0.41 (219)	2.33±0.51 (462)	<0.001
Paravalvular Aortic Regurgitation						
None	24.5% (65/265)	72.5% (392/541)	<0.001	37.0% (81/219)	79.9% (362/453)	<0.001
Trace/trivial	14.7% (39/265)	10.7% (58/541)	0.10	10.5% (23/219)	5.7% (26/453)	0.03
Mild	48.7% (129/265)	10.7% (58/541)	<0.001	38.8% (85/219)	11.3% (51/453)	<0.001
Mild-moderate	0.0% (0/265)	0.0% (0/541)	Undefined	0.0% (0/219)	0.0% (0/453)	Undefined
Moderate	7.2% (19/265)	0.4% (2/541)	<0.001	5.9% (13/219)	0.9% (4/453)	<0.001
Moderate-severe	0.0% (0/265)	0.2% (1/541)	1.00	0.9% (2/219)	0.0% (0/453)	0.11
Severe	0.0% (0/265)	0.0% (0/541)	Undefined	0.0% (0/219)	0.0% (0/453)	Undefined
AR (severity not evaluable)	4.9% (13/265)	5.5% (30/541)	0.70	6.8% (15/219)	2.2% (10/453)	0.003

Numbers are presented as % (n); outcomes were adjudicated by the CEC; aortic regurgitation grading is based on Pibarot, et al. (2015)[105]

a: From randomization to time point

b: Due to new conduction disturbances or arrhythmias; "no prior PPM" indicates subjects without a PPM before the index procedure

c: For valve-related dysfunction; surgical or interventional

d: For valve-related symptoms or worsening congestive heart failure (NYHA Class III or IV)

e: Periprocedural (≤72 hours post index procedure)

f: Includes valve migration, valve embolization, or ectopic valve deployment

g: Baseline: 0.70±0.19 cm^2 (280) for CoreValve and 0.69±0.19 cm^2 (541) for Lotus (*P*=0.33)

h: Baseline: 43.85±12.31 mmHg (294) for CoreValve and 44.64±13.35 mmHg (575) for Lotus (*P*=0.40)

Note: "Discharge" represents discharge from hospitalization or 7 days post-procedure, whichever came first.

Abbreviations: AR=aortic regurgitation; AKI=acute kidney injury; CEC=Clinical Events Committee; EOA= effective orifice area; MI=myocardial infarction; PPM=permanent pacemaker; TAV=transcatheter aortic valve; TTE=transthoracic echocardiography; VARC=Valve Academic Research Consortium

Reference: Feldman 2018[44]

In conclusion, in this large (N=912) randomized comparison of two different types of TAVR platforms, the Lotus Valve System was non-inferior to the commercially available CoreValve for the composite primary safety endpoint at 30 days. Lotus showed superiority for the composite primary effectiveness endpoint at 1 year, driven by significantly fewer disabling strokes (3.6% vs 7.1%, *P*=0.02) and significantly less moderate or severe PVR (0.9% vs 6.9%, *P*<0.0001; core lab determination). The frequency of overall stroke at 1 year was 7.0% with Lotus and 9.4% with CoreValve; the repositionability of Lotus did not lead to a higher stroke rate compared to CoreValve. Recently reported 1-year stroke rates include 5.6% among high-risk subjects in the adjudicated SAPIEN 3 registry[106] and 8.8% and 12.6% among TAVR and SAVR subjects, respectively, in the U.S. CoreValve High Risk Study[25]. Lower stroke rates have been reported in lower-risk subject groups[34,49]. Moderate or greater PVR has been associated with an increased risk of mortality[55,56]. The impact of mild PVR is less clear[57,58] although a recent meta-analysis suggested that mild PVR may also be associated with increased all-cause and cardiovascular mortality[59]. Reported rates for moderate or greater PVR with newer generation devices have ranged from 1.5% with the balloon-expandable SAPIEN 3 valve[32] to 5.3% with Evolut R[49] with lower rates in intermediate compared to high risk subjects.

There were more new pacemaker implantations (41.4% vs 23.0%, *P*<0.0001 among subjects without a prior pacemaker) at 1 year with Lotus. Pacemaker implantation is associated with subject morbidity and increased cost (including repeat hospitalization)[81] but has not been associated with decreased survival in other studies of high risk subjects[77,78,82,107]. A recently published meta-analysis found that subjects with and without PPM post TAVR had similar rates for all-cause mortality, cardiovascular mortality, MI, and stroke at 30 days and 1 year[108]. This analysis did show that improvement in LVEF was significantly greater in subjects without PPM. Valve thrombosis was uncommon but there were significantly more cases, as defined by VARC criteria, with Lotus (1.5% vs. 0%, *P*=0.03). Most were identified based on increased mean aortic gradient at protocol-directed follow-up echocardiography and all showed a decrease in mean gradient after anticoagulation therapy. These results are consistent with a recent registry report based on CT showing subclinical leaflet thrombosis rates of 4% with surgical valves and 12% with TAVR valves and suggesting that the supra-annular CoreValve may have a lower rate compared to TAVR valves with an annular location (CoreValve/Evolut R: 6%; Lotus: 14%; Edwards [Sapien, SAPIEN XT, and SAPIEN 3]: 14%; Portico: 30%)[109]. A recent single-center retrospective analysis (281 balloon-expandable, 305 self-expanding, 56 Lotus) found an overall incidence of 2.8% for clinical valve thrombosis[110]. Reported rates were 4.6% for SAPIEN valves, 1.0% for CoreValve/Evolut R, and 3.6% for Lotus. At 1 year, valve malpositioning, repeat procedures, and TAV-in-TAV deployment were all less common with Lotus. The observed rate of TAV-in-TAV with CoreValve was 2.3%; rates of TAV-in-TAV with CoreValve in prior US pivotal CoreValve trials have ranged from 1.3% to 6.7%[25,34,47,49].

Overall, outcomes in the REPRISE III RCT support the safety and efficacy of the Lotus Valve System in symptomatic subjects with severe calcific aortic stenosis who are considered extreme or high risk for surgical valve replacement.

4.1.2.5. REPRISE Japan

The objective of the REPRISE Japan clinical trial (REpositionable Percutaneous Replacement of Stenotic Aortic Valve through Implantation of Lotus™ Valve System – Clinical Evaluation in Japan; NCT02491255) was to confirm the safety and effectiveness of the Lotus™ Valve System in the Japanese medical environment for TAVR in symptomatic subjects with calcific, severe native aortic stenosis considered at high or extreme risk for SAVR. The 30-day primary safety composite endpoint includes all-cause mortality, stroke, life-threatening and major bleeding events, stage 2 or 3 acute kidney injury, and major vascular complications. The primary effectiveness endpoint is a composite at 6 months of all-cause mortality and disabling stroke and moderate or greater PVR based on core lab assessment. Other measurements incorporated the minimum data collection and endpoints recommended and defined by the VARC guidelines. Subject screening, data collection, and event assessments were as described for REPRISE II (Section **4.1.2.2**).

There were 40 evaluable subjects enrolled at 5 centers in the transfemoral arm of REPRISE Japan. The primary safety composite endpoint rate was 15.0% (6/40) at 30 days and the primary effectiveness composite endpoint was 5.3% (2/38) at 6 months. **Table 4.1-12** shows clinical and echocardiographic outcomes at 30 days, 6 months, and 1 year. Mortality through 1 year was low (7.5%) as was disabling stroke (2.5%). There was no moderate or severe PVR. Overall, outcomes were similar to that seen with Lotus in REPRISE II (Section **4.1.2.2**) and REPRISE III (Section **4.1.2.4**) and demonstrated consistent safety and effectiveness results with the Lotus Valve System in Japanese subjects.

Table 4.1-12: 30-Day, 6-Month, and 1-Year Outcomes – REPRISE Japan Evaluable Transfemoral Cohort (N=40)

Outcomes	30 Days	6 Months	1 Year
Clinical Outcomes (CEC Adjudicated, VARC Definitions)			
All-cause mortality	0.0% (0/40)	2.5% (1/40)	7.5% (3/40)
Cardiovascular	0.0% (0/40)	2.5% (1/40)	5.0% (2/40)
All stroke	7.5% (3/40)	7.5% (3/40)	7.5% (3/40)
Disabling stroke	2.5% (1/40)	2.5% (1/40)	2.5% (1/40)
Major vascular complications	2.5% (1/40)	2.5% (1/40)	2.5% (1/40)
Life-threatening or disabling bleeding	5.0% (2/40)	5.0% (2/40)	5.0% (2/40)
Major bleeding	0.0% (0/40)	0.0% (0/40)	0.0% (0/40)
Myocardial infarction	0.0% (0/40)	0.0% (0/40)	0.0% (0/40)
Acute kidney injury – Stage 2 or 3[a]	0.0% (0/40)	0.0% (0/40)	0.0% (0/40)
New PPM implantation[b]	22.5% (9/40)	22.5% (9/40)	25.0% (10/40)
New PPM in subjects without prior PPM	23.7% (9/38)	23.7% (9/38)	26.3% (10/38)
Coronary obstruction (periprocedural)	0.0% (0/40)	0.0% (0/40)	0.0% (0/40)
Ventricular septal perforation (periprocedural)	0.0% (0/40)	0.0% (0/40)	0.0% (0/40)
Mitral apparatus damage (periprocedural)	0.0% (0/40)	0.0% (0/40)	0.0% (0/40)
Cardiac tamponade (periprocedural)	0.0% (0/40)	0.0% (0/40)	0.0% (0/40)
Valve-related dysfunction[c]	0.0% (0/40)	0.0% (0/40)	0.0% (0/40)
Hospitalization[d]	0.0% (0/40)	0.0% (0/40)	0.0% (0/40)

Table 4.1-12: 30-Day, 6-Month, and 1-Year Outcomes – REPRISE Japan Evaluable Transfemoral Cohort (N=40)

Outcomes	30 Days	6 Months	1 Year
Atrial fibrillation – new onset	5.0% (2/40)	5.0% (2/40)	5.0% (2/40)
Atrial flutter – new onset	0.0% (0/40)	0.0% (0/40)	0.0% (0/40)
Prosthetic aortic valve malpositioning[e]	0.0% (0/40)	0.0% (0/40)	0.0% (0/40)
TAV-in-TAV deployment	0.0% (0/40)	0.0% (0/40)	0.0% (0/40)
Prosthetic aortic valve thrombosis	0.0% (0/40)	0.0% (0/40)	0.0% (0/40)
Prosthetic aortic valve endocarditis	0.0% (0/40)	0.0% (0/40)	0.0% (0/40)
Valve Performance by TTE (Core Lab Assessment)			
Aortic valve area (effective orifice area) (cm^2)[f]	1.54±0.37 (40)	1.49±0.38 (35)	1.38±0.31 (35)
Mean aortic valve gradient (mmHg)[g]	13.04±4.87 (40)	13.40±5.65 (37)	14.22±6.09 (35)
Peak aortic gradient (mmHg)	21.81±8.39 (40)	22.69±9.26 (37)	24.44±10.61 (35)
Peak aortic velocity (cm/s)	2.30±0.43 (40)	2.34±0.45 (37)	2.42±0.51 (36)
Paravalvular Aortic Regurgitation			
None	60.0% (24/40)	75.7% (28/37)	75.0% (27/36)
Trace/trivial	10.0% (4/40)	10.8% (4/37)	8.3% (3/36)
Mild	27.5% (11/40)	13.5% (5/37)	16.7% (6/36)
Mild-moderate	0.0% (0/40)	0.0% (0/37)	0.0% (0/36)
Moderate	0.0% (0/40)	0.0% (0/37)	0.0% (0/36)
Moderate-severe	0.0% (0/40)	0.0% (0/37)	0.0% (0/36)
Severe	0.0% (0/40)	0.0% (0/37)	0.0% (0/36)

Numbers are presented as % (count/sample size) or mean±SD (n). Data are from the intent-to-treat analysis set; aortic regurgitation grading is based on Pibarot, et al. (2015)[105].
a: AKIN Stage 2 or Stage 3 (including renal replacement therapy)[111,112]; ≤ 7 days post index procedure
b: Resulting from new or worsened conduction disturbances
c: Requiring repeat procedure (surgical or interventional)
d: For valve-related symptoms or worsening congestive heart failure
e: Including valve migration, valve embolization, ectopic valve deployment (procedural)
f: Baseline effective orifice area (cm^2): 0.58 ± 0.20 (39)
g: Baseline mean aortic gradient (mmHg): 57.31 ± 20.16 (40)
Abbreviations: CEC=clinical events committee; PPM=permanent pacemaker; TAV=transcatheter aortic valve; TTE=transthoracic echocardiography; VARC=Valve Academic Research Consortium
Reference: Saito 2017[113], 2018[114]

4.1.2.6. REPRISE NG DS Study

The REpositionable Percutaneous Replacement of Stenotic Aortic Valve through Implantation of LotuS ValvE with the Next Generation Delivery System (REPRISE NG DS) study (NCT02329496) is a first-human-use trial evaluating a modified version of the delivery system that was studied in REPRISE I, REPRISE II, REPRISE III, and RESPOND. In Cohort A of this prospective single-arm study, 10 subjects were enrolled at 2 investigative centers in Australia; the device was introduced into the body using the Lotus Introducer Set. In Cohort B, an additional 7 subjects were enrolled at the same centers to evaluate acute performance and safety of a further optimized version of the LOTUS *Edge* device (including

radiopaque markers on the valve locking assembly). Cohort B also assessed the acute performance and safety of an early iteration of the iSleeve™ Introducer Set and its compatibility with the LOTUS *Edge* device. A third cohort (Cohort C) subsequently enrolled 21 subjects who were treated with a further refined version of the LOTUS *Edge* delivery system. In some Cohort C subjects a further refined version of the iSleeve Introducer was used. The primary endpoint in REPRISE NG DS is technical success, defined as follows: successful vascular access, delivery and deployment of the Lotus valve and successful retrieval with the Lotus NG delivery system; correct positioning of the Lotus valve in the proper anatomical location; and a single Lotus valve implanted in the proper anatomical location. Clinical follow-up will extend through 1 year.

The primary endpoint was achieved in 10/10 subjects in Cohort A[115], 5/7 in Cohort B (in 1 subject a valve was not implanted and in 1 subject a valve was implanted using the current Lotus Valve System), and 21/21 in Cohort C[116]. **Table 4.1-13** shows core lab analyses of prosthetic valve performance as assessed by TTE at discharge/7 days post procedure (secondary endpoint) and valve function at 30 days and 1 year for the 3 cohorts. In all cohorts, mean aortic valve area and mean gradient improved at discharge and remained improved at 30 days and 1 year. There were no cases of moderate or severe PVR at discharge, 30 days, or 1 year in any cohort; the majority of patients had no PVR or trace PVR at all time points. **Table 4.1-14** shows rates of CEC-adjudicated VARC-defined events through discharge/7 days, 30 days, 6 months, and 1 year. In Cohort A, one subject experienced the majority of events and subsequently died on day 13 post implant. In Cohort B, events were minimal. In Cohort C, new permanent pacemakers were placed in 2 subjects by 1 year for a rate of 9.5% (2/21) among all subjects and 11.1% (2/18) among subjects without a prior pacemaker. In summary, outcomes to 1 year in the REPRISE NG DS study demonstrate acceptable performance and safety of the Lotus valve with the next generation delivery system.

Table 4.1-13: Valve Performance by TTE, Core Lab Analysis – REPRISE NG DS Cohorts A, B and C

Measure	Cohort A (N=10)				Cohort B (N=6)				Cohort C (N=21)			
	Baseline	Discharge	30 Days	1 Year	Baseline	Discharge	30 Days	1 Year	Baseline	Discharge	30 Days	1 Year
EOA (cm^2)	0.69±0.21 (10)	1.55±0.43 (10)	1.44±0.45 (9)	1.38±0.49 (6)	0.54±0.14 (6)	1.72±0.39 (4)	1.30±0.42 (5)	1.40±0.32 (5)	0.63±0.19 (21)	1.50±0.37 (21)	1.28±0.36 (21)	1.47±0.43 (20)
Mean gradient (mmHg)	48.5±13.3 (10)	13.4±4.3 (10)	15.7±8.0 (9)	15.8±9.2 (6)	51.3±14.5 (6)	10.1±3.9 (6)	10.5±0.9 (5)	12.9±2.0 (5)	51.3±9.5 (21)	14.0±4.4 (21)	14.7±5.6 (21)	14.1±5.1 (20)
Paravalvular Aortic Regurgitation												
None	N/A	80.0 (8)	66.7 (6)	66.7 (4)	N/A	83.3 (5)	60.0 (3)	100.0 (5)	N/A	95.2 (20)	85.7 (18)	75.0 (15)
Trace	N/A	10.0 (1)	11.1 (1)	33.3 (2)	N/A	20.0 (1)	40.0 (2)	0.0 (0)	N/A	4.8 (1)	9.5 (2)	20.0 (4)
Mild	N/A	10.0 (1)	11.1 (1)	0.0 (0)	N/A	0.0 (0)	0.0 (0)	0.0 (0)	N/A	0.0 (0)	4.8 (1)	5.0 (1)
Moderate	N/A	0.0 (0)	0.0 (0)	0.0 (0)	N/A	0.0 (0)	0.0 (0)	0.0 (0)	N/A	0.0 (0)	0.0 (0)	0.0 (0)
Severe	N/A	0.0 (0)	0.0 (0)	0.0 (0)	N/A	0.0 (0)	0.0 (0)	0.0 (0)	N/A	0.0 (0)	0.0 (0)	0.0 (0)

Numbers are presented as mean±standard deviation (n) or % (n); only subjects who received a study valve are included in the core lab analyses.
Note: "Discharge" represents discharge from hospitalization or 7 days post-procedure, whichever came first.
Abbreviations: EOA=effective orifice area; N/A=not applicable; NGDS=Next Generation Delivery System; TTE=transthoracic echocardiography

Table 4.1-14: Discharge, 30-Day, 6-Month, and 1-Year Clinical Outcomes in REPRISE NG DS Cohorts A, B and C

VARC Event	Cohort A (N=10)				Cohort B (N=6)				Cohort C (N=21)			
	Discharge	30-Day	6-Month	1-Year	Discharge	30-Day	6-Month	1-Year	Discharge	30-Day	6-Month	1-Year
All-cause mortality	0.0 (0)	10.0 (1)	20.0 (2)	20.0 (2)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
Cardiovascular	0.0 (0)	10.0 (1)	10.0 (1)	10.0 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
Stroke	10.0 (1)	10.0 (1)	10.0 (1)	10.0 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	4.8 (1)	4.8 (1)	4.8 (1)	4.8 (1)
Disabling stroke	10.0 (1)	10.0 (1)	10.0 (1)	10.0 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	4.8 (1)	4.8 (1)	4.8 (1)	4.8 (1)
Major vascular complications	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	9.5 (2)	9.5 (2)	9.5 (2)	9.5 (2)
New PPM[a]	30.0 (3)	40.0 (4)	30.0 (3)	40.0 (4)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	9.5 (2)[b]	9.5 (2)[b]	9.5 (2)[b]	9.5 (2)[b]
Life-threatening/ disabling bleeding	20.0 (2)	20.0 (2)	20.0 (2)	20.0 (2)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
MI	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	9.5 (2)
AKI – Stage 2/3	10.0 (1)	10.0 (1)	10.0 (1)	10.0 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
Repeat procedure[c]	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)

Table 4.1-14: Discharge, 30-Day, 6-Month, and 1-Year Clinical Outcomes in REPRISE NG DS Cohorts A, B and C

VARC Event	Cohort A (N=10)				Cohort B (N=6)				Cohort C (N=21)			
	Discharge	30-Day	6-Month	1-Year	Discharge	30-Day	6-Month	1-Year	Discharge	30-Day	6-Month	1-Year
Hospitalization[d]	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	16.7 (1)	16.7 (1)	0.0 (0)	0.0 (0)	0.0 (0)	9.5 (2)
New onset atrial fibrillation/flutter	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	9.5 (2)	9.5 (2)	9.5 (2)	9.5 (2)
Coronary obstruction[e]	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
Ventricular septal perforation[e]	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
Mitral apparatus damage[e]	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
Cardiac tamponade[e]	10.0 (1)	10.0 (1)	10.0 (1)	10.0 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
Prosthetic aortic valve malapposition[f]	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
Prosthetic aortic valve thrombosis	0.0 (0)	0.0 (0)	0.0 (0)	10.0 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	4.8 (1)	4.8 (1)	4.8 (1)
Prosthetic aortic valve endocarditis	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	16.7 (1)	16.7 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)

Numbers are presented as % (n); outcomes were adjudicated by the CEC; ITT analysis set for Cohorts A and C; as-treated analysis set for Cohort B

a: Due to new conduction disturbances or arrhythmias

b: In Cohort C, the rate of new PPM implantation among subjects without a prior pacemaker was 11.1%.

c: For valve-related dysfunction (surgical/interventional)

d: For valve-related symptoms or worsening congestive heart failure

e: Periprocedural (≤72 hours post index procedure)

f: Includes valve migration, valve embolization, ectopic valve deployment, or TAV-in-TAV

Note: "Discharge" represents discharge from hospitalization or 7 days post-procedure, whichever came first.

Note: In Cohort A, one subject experienced the majority of events and died on day 13. In Cohort B, there were 2 procedural minor access site related vascular complications and 1 procedural major bleeding event. In Cohort C, there were 2 minor access site related vascular complications and 2 major bleeding events.

Abbreviations: AKI=acute kidney injury; CEC=Clinical Events Committee; ITT=intention-to-treat; MI=myocardial infarction; NGDS=Next Generation Delivery System; PPM=permanent pacemaker; TAV=transcatheter aortic valve; VARC=Valve Academic Research Consortium

4.1.2.7. REPRISE EDGE

The prospective, single-arm REpositionable Percutaneous Replacement of NatIve StEnotic Aortic Valve through Implantation of LOTUS EDGE Valve System – Evaluation of Performance and Safety study (REPRISE EDGE; NCT02854319; N=15) has the same overall study design as REPRISE NG DS (Section **4.1.2.6**) and assessed acute performance and safety of the same LOTUS *Edge* design that was used in Cohort C. The primary endpoint was the mean aortic valve pressure gradient at discharge as measured by echocardiography and assessed by an independent core laboratory. Secondary endpoints included technical success and device performance peri- and post-procedure based in part on VARC criteria.

At discharge, the mean aortic gradient was 14.4±4.1 mmHg (N=15). Technical success was 100% and all attempts at repositioning or retrieving the valve were successful, and there was no moderate or severe PVR at discharge. **Table 4.1-15** shows clinical and echocardiographic outcomes at 30 days and 1 year. There was no mortality and 1 disabling stroke through 1 year; PPM were placed in 2 subjects by 30 days for a rate of 13.3% among subjects without a prior PPM. Mean aortic valve area and mean gradient were improved at 30 days and 1 year with no moderate or severe PVR. Overall, outcomes with LOTUS Edge are consistent with outcomes observed in REPRISE II/II Extension and REPRISE III and with other TAVR studies using the VARC metrics.

Table 4.1-15: 30-Day and 1-Year Outcomes – REPRISE EDGE (N=15)

Outcomes	30 Days	1 Year
Clinical Outcomes (CEC Adjudicated, VARC Definitions)		
All-cause mortality	0.0% (0/15)	0.0% (0/15)
All stroke	6.7% (1/15)	6.7% (1/15)
Disabling stroke	6.7% (1/15)	6.7% (1/15)
Major vascular complications	20.0% (3/15)	20.0% (3/15)
Life-threatening or disabling bleeding	13.3% (2/15)	13.3% (2/15)
Major bleeding	20.0% (3/15)	20.0% (3/15)
Acute kidney injury – Stage 2 or 3[a]	0.0% (0/15)	0.0% (0/15)
New PPM implantation[b]	13.3% (2/15)	20.0% (3/15)
New PPM in subjects without prior pacemaker	13.3% (2/15)	20.0% (3/15)
Coronary obstruction (periprocedural)	0.0% (0/15)	0.0% (0/15)
Ventricular septal perforation (periprocedural)	0.0% (0/15)	0.0% (0/15)
Mitral apparatus damage (periprocedural)	0.0% (0/15)	0.0% (0/15)
Cardiac tamponade (periprocedural)	0.0% (0/15)	0.0% (0/15)
Myocardial infarction	0.0% (0/15)	0.0% (0/15)
Valve-related dysfunction requiring repeat procedure[c]	0.0% (0/15)	0.0% (0/15)
Hospitalization for valve-related symptoms or worsening CHF	0.0% (0/15)	0.0% (0/15)
Atrial fibrillation or atrial flutter (new onset)	0.0% (0/15)	0.0% (0/15)
Prosthetic aortic valve malpositioning[d]	0.0% (0/15)	0.0% (0/15)
TAV-in-TAV deployment	0.0% (0/15)	0.0% (0/15)
Prosthetic aortic valve thrombosis	0.0% (0/15)	6.7% (1/15)
Prosthetic aortic valve endocarditis	0.0% (0/15)	6.7% (1/15)

Table 4.1-15: 30-Day and 1-Year Outcomes – REPRISE EDGE (N=15)

Outcomes	30 Days	1 Year
Valve Performance by Transthoracic Echocardiography (Core Lab Assessment)		
Aortic valve area (effective orifice area) (cm^2)[e]	1.24±0.29 (13)	1.38±0.34 (11)
Mean aortic valve gradient (mmHg)[f]	14.95±8.40 (15)	12.98±4.52 (14)
Peak aortic gradient (mmHg)	25.65±12.50 (15)	23.64±8.55 (14)
Peak aortic velocity (cm/s)	2.47±0.57 (15)	2.39±0.42 (14)
Paravalvular Aortic Regurgitation		
None	66.7% (10/15)	71.4% (10/14)
Trace/trivial	13.3% (2/15)	28.6% (4/14)
Mild	13.3% (2/15)	0.0% (0/14)
Mild-moderate	0.0% (0/15)	0.0% (0/14)
Moderate	0.0% (0/15)	0.0% (0/14)
Moderate-severe	0.0% (0/15)	0.0% (0/14)
Severe	0.0% (0/15)	0.0% (0/14)

Values are % (count/sample size) or mean±SD (n). Data are from the per-protocol analysis set (enrolled subjects implanted with a LOTUS Edge valve); aortic regurgitation grading is based on Pibarot, et al. (2015)[105].

a: AKIN Stage 2 or Stage 3 (including renal replacement therapy); ≤ 7 days post index procedure

b: Resulting from new or worsened conduction disturbances

c: Surgical or interventional

d: Including valve migration, valve embolization, ectopic valve deployment (procedural)

e: Baseline effective orifice area (cm^2): 0.64 ± 0.19 (10)

f: Baseline mean aortic gradient (mmHg): 49.46 ± 16.01 (13)

Abbreviations: CEC=clinical events committee; CHF=congestive heart failure; PPM=permanent pacemaker; TAV=transcatheter aortic valve; VARC=Valve Academic Research Consortium

4.2. *Study Rationale*

As noted above, the Lotus Valve System potentially provides a number of performance and safety features beyond that of earlier TAVR devices. These include an enhanced ability to place the valve correctly at the first attempt, the capacity to reposition the device if the initial deployment is considered to be suboptimal, the ability to retrieve the device if during the procedure a decision is made to replace it with another valve to optimize implant or not to implant, and the aforementioned outer seal designed to minimize PVR. Because the investigational device, the LOTUS *Edge* Valve System, consists of essentially the same pre-loaded, stent-mounted tissue valve prosthesis as the Lotus Valve System evaluated in the REPRISE I, REPRISE II, REPRISE III, REPRISE Japan, and RESPOND studies but with a catheter delivery system designed for improved deliverability (evaluated in the REPRISE NG DS and REPRISE EDGE studies) the anticipated benefits and risks are very similar. The valve component with the addition of tantalum (radiopaque) markers is also intended to enhance locking visualization. Like the Lotus Introducer, the iSleeve Introducer Set has a dilator and sheath component, but the iSleeve sheath is expandable. This allows for transient sheath expansion during delivery system introduction, enabling expanded vascular access

and reducing the duration of time the access vessel is expanded and therefore minimizing potential for vessel trauma. Both sheaths have a hydrophilic coating that when activated increases the lubricity of the surface to aid in delivery.

The anticipated risks and benefits associated with use of the LOTUS *Edge* Valve System, with either the Lotus or iSleeve Introducer Sets, by trained physicians with extensive TAVR experience, and with participation in this clinical investigation are summarized in the Investigator Brochure and in Section **18** of this document. The conclusion of this risk-benefit analysis demonstrates that the known risks associated with the procedure, and specifically the use of the LOTUS *Edge* Valve System, have been mitigated to acceptable limits, which are comparable to that for existing transcatheter aortic valves. It was also concluded that the aforementioned design features may improve procedural safety and longer term clinical outcomes. No new hazards/harms are introduced by the LOTUS *Edge* Valve System compared to the Lotus Valve System when used with either the Lotus or iSleeve Introducer Sets and the overall risk profile of the device has not changed. The available Sponsor-provided training program and proctorship for physicians further mitigates any residual risk. The result is a procedure with residual subject risk comparable to that of currently available transcatheter aortic valves and potential benefit compared with other alternatives.

It is therefore determined that:

- All applicable risks have been addressed through appropriate testing and any residual risks are acceptable when weighed against the potential benefits to the subject.
- The potential benefits of the use of the device out-weigh the risks.

5. Device Description

The investigational LOTUS *Edge*™ Valve System is intended to improve aortic valve function for symptomatic subjects with severe aortic stenosis who are at intermediate risk for standard surgical aortic valve replacement (SAVR), including those who have a bicuspid native valve.

5.1. *LOTUS Edge Valve System*

The Lotus™ Valve System and LOTUS *Edge* Valve System are both made up of two principal elements: a bioprosthetic aortic valve implant and a catheter-based delivery system for introduction and delivery of the valve implant (**Figure 5.1-1**). The device is introduced percutaneously using conventional catheterization techniques. Access using a surgical cut-down approach can also be performed to gain arterial access. Valve sizes include 23mm, 25mm, and 27mm diameter. The Lotus family of devices provides a number of important performance and safety features beyond what is currently offered with first generation TAVR systems. Some of these improvements include the ability to reposition the device if the initial deployment is considered to be suboptimal and the ability to retrieve the device during the procedure if necessary. The LOTUS *Edge* Valve System is a design iteration of the Lotus Valve System, which was assessed in the REPRISE I, REPRISE II, REPRISE Japan,

REPRISE III, and RESPOND studies (Section **4.1.2**). The LOTUS *Edge* Valve System has a catheter delivery system with enhanced deliverability and tantalum (radiopaque) markers have been added to the valve locking assembly (i.e., buckle and post-top components) to aid visualization of locking during the procedure. The LOTUS *Edge* Valve System also incorporates a modified leadscrew component, referred to as the Depthguard™ technology, which results in a slightly decreased rate of retraction of the outer sheath, during valve deployment compared to the Lotus Valve System. Detailed product information can be found in the IFU and in the Investigator's Brochure.

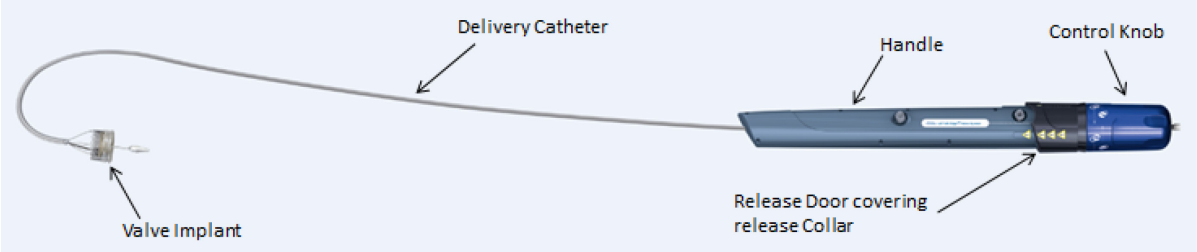


Figure 5.1-1: Overview of Principal Components of the LOTUS *Edge* Valve System

5.1.1. LOTUS *Edge* Valve

The LOTUS *Edge* valve is shown in **Figure 5.1-2**. It 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 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. Radiopaque markers on the post-top and buckle components aid visualization during the locking procedure. The Adaptive Seal™ is made of a polyurethane/polycarbonate blend and is located on the outside bottom half of the frame. This seal provides a barrier between the existing 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. The valve is available in three sizes: 23mm, 25mm, and 27mm. The frame height of all three valve sizes in the deployed state is approximately 19 mm.

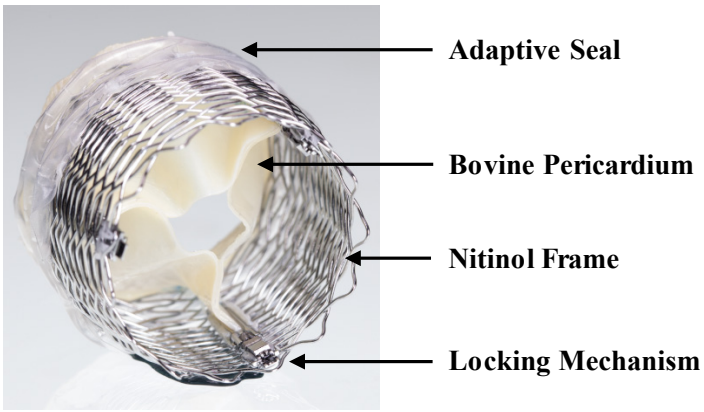


Figure 5.1-2: LOTUS *Edge* Valve Implant

5.1.2. LOTUS *Edge* Delivery System

The LOTUS *Edge* Delivery System is composed of 3 main assemblies: (1) an inner catheter assembly (referred to as the multi-lumen catheter), which is attached to the valve implant; (2) an outer catheter assembly (referred to as the outer sheath); and (3) a controller assembly, which is used to control placement and release of the valve. Changes between the Lotus Valve System and the LOTUS *Edge* Valve System are described in the Investigator Brochure.

The controller assembly is shown in **Figure 5.1-3** (locked configuration in the top image). The principal control used to deploy the valve is the control knob at the proximal end of the controller. This control knob is used to first unsheathe the device and deploy the implant into the intermediate functioning, but non-locked, configuration and subsequently to shorten the implant and lock it in the final, anchored configuration. The process can be reversed to unlock the device or recapture the implant inside the outer sheath. When the valve implant is successfully positioned and locked in the desired location the delivery system is permanently detached. Additional information on valve implantation and release is found in the IFU.

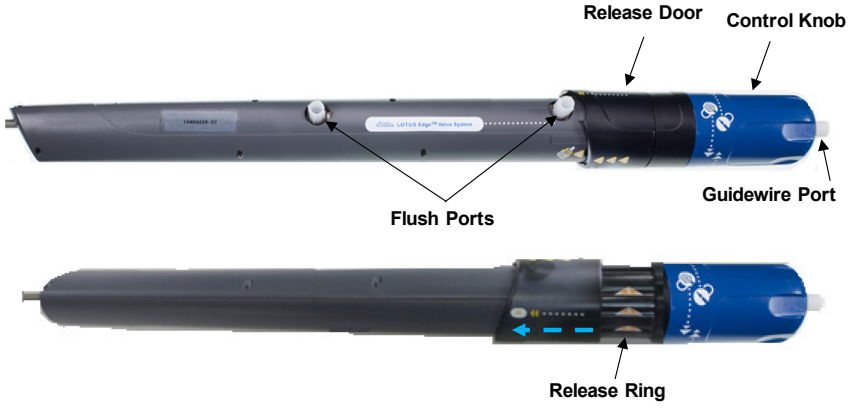


Figure 5.1-3: LOTUS *Edge* Controller

Top: Locked configuration. Bottom: Door pulled forward allowing the valve to be released

5.1.3. Lotus and iSleeve Introducer Sets

The large Lotus Introducer Set or, when available, the iSleeve Introducer Set (**Figure 5.1-4**) will be used as an accessory to the LOTUS *Edge* Valve System during the procedure. In countries where the introducer sets are approved, the commercial devices will be used. In countries where they are not approved, they will be considered investigational devices. They both include a dilator and an introducer sheath with a hydrophilic coating that, when activated, increases the lubricity of the surface to aid in delivery. The large Lotus Introducer is intended for use with the 23mm, 25mm, or 27mm LOTUS *Edge* valve in subjects with femoral vascular access ≥6.5 mm. The sheath component of the iSleeve is expandable, which allows for transient sheath expansion during delivery system introduction. Temporary expansion of the access vessel reduces the time the access vessel is expanded during device introduction and therefore potentially reduces vessel trauma. The 15F iSleeve is capable of introducing the 23mm, 25mm and 27mm LOTUS *Edge* valve sizes into subjects with femoral vascular access ≥5.9 mm.

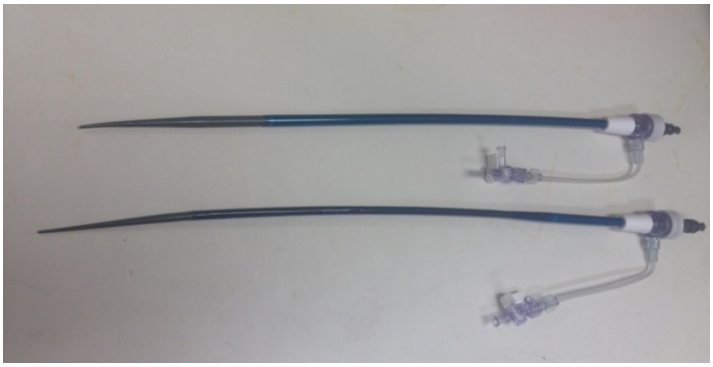


Figure 5.1-4: Lotus Introducer Set (Top) and iSleeve Introducer Set (Bottom)

Detailed information can be found in the respective Instructions For Use.

5.2. *Device Labeling*

The study Manual of Operations includes the IFUs for the LOTUS *Edge* Valve System and, when available, the iSleeve Introducer Set. Study devices are labeled on the top and one side (one label wraps around the top and side) of the outer carton and on the sterile pouch. Packaging will include peelable, self-adhesive labels for each unit shipped. The labeling will include the following information.

- Product Name
- Unique identifier
- Lot number/Serial number
- Expiration (use by) date (labeled as month/year, device not to be used after the last day of the indicated month)

The following statement appears on the label.

Caution: Investigational Device. Limited by Federal Law (USA) to Investigational Use.

In addition, the following statements appear on the product labeling.

CAUTION: Exclusively for Clinical Investigations.

The IFU for the large Lotus Introducer Set will also be provided in the study Manual of Operations. The label will also include the above, with the exception of the investigational device statement for countries where the device is commercially available.

6. Study Objectives and Endpoints

6.1. *Study Objectives*

The objective of the REPRISE IV trial is to evaluate the safety and effectiveness of the LOTUS *Edge* Valve System when used with the Lotus or iSleeve Introducer Set for transcatheter aortic valve replacement (TAVR) in symptomatic subjects with severe aortic stenosis who are considered at intermediate risk for surgical valve replacement, including those who have a bicuspid native valve.

6.2. *Study Endpoints*

Outcomes will be assessed on an intention-to-treat (ITT) basis and an implanted basis. The ITT analysis population includes all subjects who sign the Informed Consent Form (ICF; see Section **20**) and are enrolled in the trial (see Section **9.1** for point of enrollment), regardless of whether a study valve is implanted. The implanted analysis population includes ITT subjects who are implanted with the study valve. Endpoint definitions can be found in **Table 25.2-1**.

6.2.1. Primary Endpoint

The primary endpoint is a composite of all-cause mortality and all stroke at 1 year. The primary analysis set for the primary endpoint is the ITT analysis set.

6.2.2. Additional Measurements

Additional measurements based on the VARC endpoints and definitions[61,62] (see ***Note 1*** below) will be collected peri- and post-procedure, at discharge or 7 days post-procedure (whichever comes first), 30 days, and annually up to 10 years post index procedure, unless otherwise specified below.

- Safety endpoints adjudicated by an independent Clinical Events Committee (CEC; Section **21.1.1**):
  - Mortality: all-cause, 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) and major (through 5 years)
- Acute kidney injury (AKI; ≤7 days post index procedure): based on the AKIN System[111,112] Stage 3 (including renal replacement therapy) or Stage 2
- Major vascular complication (including annular rupture; through 5 years)
- Repeat procedure for valve-related dysfunction (surgical or interventional therapy)
- Hospitalization for valve-related symptoms or worsening CHF (NYHA class III or IV)
- New permanent pacemaker implantation resulting from new or worsened conduction disturbances (definitions in Table 25.2-1; see ***Note 2*** below)
- New onset of atrial fibrillation or atrial flutter
- Coronary obstruction: periprocedural (≤72 hours post index procedure)
- Ventricular septal perforation: periprocedural (≤72 hours post index procedure)
- Mitral apparatus damage: periprocedural (≤72 hours post index procedure)
- Cardiac tamponade: periprocedural (≤72 hours post index procedure)
- Prosthetic aortic valve malpositioning, including valve migration, valve embolization, or ectopic valve deployment
- Transcatheter aortic valve (TAV)-in-TAV deployment
- Prosthetic aortic valve thrombosis
- Prosthetic aortic valve endocarditis

- Device performance endpoints peri- and post-procedure:
  - Successful vascular access, delivery and deployment of the study valve and successful retrieval of the delivery system
  - Successful retrieval of the study valve if retrieval is attempted
  - Successful repositioning of the study valve if repositioning is attempted (see ***Note 3*** below)
  - Grade of aortic valve regurgitation: paravalvular, central and combined; the overall distribution of paravalvular aortic regurgitation (none, trace/trivial, mild, moderate, severe) will be determined as well as the percentage of subjects who have moderate or severe paravalvular regurgitation and the percentage of subjects who have mild, moderate or severe paravalvular regurgitation
- Device success, defined as absence of procedural mortality, correct positioning of a single transcatheter valve into the proper anatomical location , intended performance of the study device (effective orifice area [EOA] >0.9 cm^2 for BSA <1.6 m^2 and EOA >1.1 cm^2 for BSA ≥1.6 m^2 plus either a mean aortic valve gradient <20 mm Hg or a peak velocity <3m/sec, and no moderate or severe prosthetic valve aortic regurgitation)
- Additional indications of prosthetic aortic valve performance as measured by transthoracic echocardiography (TTE; see ***Note 4*** and ***Note 5*** below) and assessed by an

independent core laboratory, including EOA, mean and peak aortic gradients, peak aortic velocity, and grade of aortic regurgitation

- Functional status as evaluated by the following:
  - 5-m gait speed test[117] (at 1 year compared to baseline)
  - New York Heart Association (NYHA) classification (see ***Note 5*** below)
- Neurological status (see ***Note 6*** below) as determined by the following:
  - National Institutes of Health Stroke Scale (NIHSS; performed by a neurology professional or certified personnel) at discharge and 1 year
  - Modified Rankin Scale (mRS; performed by a neurology professional or certified personnel) at all follow-up visits up to 5 years
- Health status as evaluated by Kansas City Cardiomyopathy[118] and SF-12[119] Quality of Life (QOL) questionnaires at baseline, 1 month, and 1 and 5 years.
- For subjects in the Bicuspid Nested Registry, a computed tomography scan at 30 days post LOTUS *Edge* Valve implantation. The data will be evaluated by an independent CT core laboratory.
- For subjects in the CT Imaging Substudy, a 4D CT scan at 30 days and at 1 year post LOTUS *Edge* valve implantation to assess the prevalence of reduced leaflet mobility and its relationship, if any, to clinical events. The data will be evaluated by an independent CT core laboratory.

Note 1: The most current VARC definitions and endpoints available at the beginning of the trial were used.

Note 2: Clinical indications for permanent pacemaker implantation are outlined in the ACCF/AHA/HRS Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities[120]. Permanent pacemaker implantation should generally be performed only for accepted Class I indications.

Note 3: For the LOTUS *Edge* Valve System, repositioning (see definition in **Table 25.2-1**) may be achieved with partial or full resheathing (see definitions in **Table 25.2-1**) of the valve; the proportion of subjects with partial valve resheathing and full valve resheathing will be determined.

Note 4: At least 1 echocardiogram must be obtained before discharge or 7 days (whichever comes first); if multiple echocardiographic studies are performed prior to discharge and within 7 days of the procedure, the latest study performed will be used for analysis.

Note 5: Echocardiography and NYHA assessment are not required in years 6, 8, and 9 (telephone follow-up only).

Note 6: For subjects diagnosed with a stroke, a neurological physical exam (conducted by a neurologist, neurology fellow, neurology physician assistant, or neurology nurse practitioner), NIHSS assessment, and mRS must be performed after the event. Additionally, mRS must be administered at 90±14 days after a stroke (see **Table 10.1-1**). If a subject who

has not received a study device experiences a stroke within the first 1 year after the index procedure, mRS must be performed on that subject after the event; mRS must also be administered at 90±14 days after a stroke and the results must be reported to the Sponsor. The simplified mRS questionnaire may be used for this follow-up assessment.

6.3. *Overview of Objectives and Endpoints*

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

Table 6.3-1: Overview of Objectives and Endpoints

Objective	Endpoint	Rationale for Endpoint
Primary Endpoint		
Evaluate safety and effectiveness of the valve implant	1-Year Composite: all-cause mortality and all stroke	Critical safety events that are observed in the elderly population undergoing TAVR; assessments recommended by VARC[61,62]; assess the long-term benefit (1 year) in a large elderly population. Events are adjudicated by an independent CEC.
Additional Measurements of Safety and Effectiveness		
Evaluate safety of the valve implant and the procedure	Safety measures at discharge, 30 days, and annually up to 10 years post index procedure	Safety assessments recommended by VARC[61,62] for this elderly population. Events are adjudicated by an independent CEC.
Evaluate effectiveness of the valve implant	Effectiveness measures at discharge, 30 days, and annually up to 10 years post index procedure	Effectiveness assessments recommended by VARC[61,62] for this elderly population. Events are adjudicated by an independent CEC.

Abbreviations: CEC=Clinical Events Committee; VARC=Valve Academic Research Consortium

7. Study Design

7.1. *Scale and Duration*

The REPRISE IV clinical study includes a prospective, multicenter, single-arm trial (Main Cohort; N=696) designed to evaluate the safety and effectiveness of the LOTUS *Edge* Valve System when used with the Lotus™ Introducer Set or, when available, the iSleeve™ Introducer Set for TAVR in symptomatic subjects who have severe aortic stenosis and who are at intermediate risk for SAVR. There will be a roll-in phase (up to 130 subjects) for centers that do not have previous experience implanting the LOTUS *Edge* Valve. There will also be a single-arm nested registry cohort of subjects who have a bicuspid native valve to assess safety and effectiveness (Bicuspid Nested Registry; N=100). Selected centers with the ability to perform high quality 4D computed tomography (CT) scans will include up to 200 subjects from the Main Cohort in a CT Imaging Substudy to assess the prevalence of reduced leaflet mobility and its relationship, if any, to clinical events. All subjects in these

centers will be approached for consent to participate in the CT study. If 200 subjects have not enrolled in the CT Imaging Substudy by completion of enrollment in the main cohort, additional subjects who meet the REPRISE IV eligibility criteria will be enrolled in a separate CT Imaging Cohort to achieve a total of 200 subjects in the CT Imaging Substudy. **Figure 7.1-1** shows the study design.

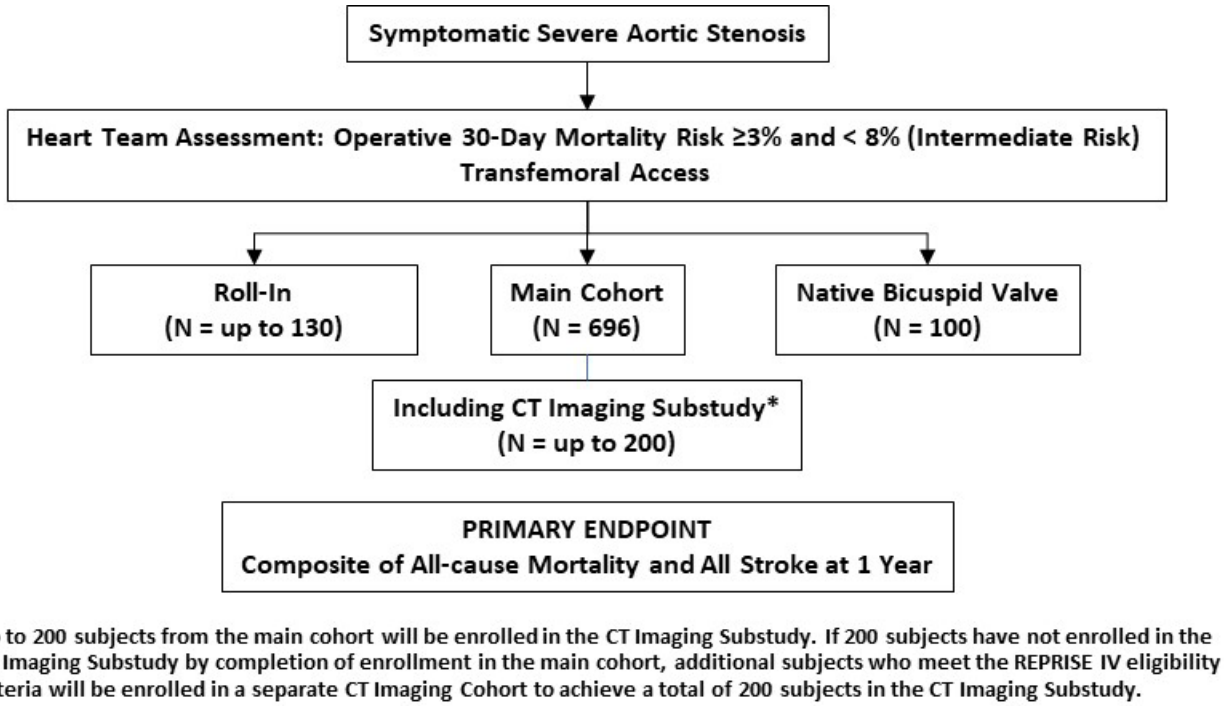


Figure 7.1-1: REPRISE IV Study Design

All subjects implanted will be followed at baseline, peri- and post-procedure, at discharge or 7 days post-procedure (whichever comes first), 30 days, and then annually for up to 10 years post-procedure. Enrolled subjects who do not have a study device implanted will be assessed through 1 year post procedure for safety/adverse events.

The REPRISE IV study will be conducted in accordance with 21 CFR Parts 11, 50, and 54; the relevant parts of the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practices (GCP); the International Standard ISO 14155 Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice; ethical principles that have their origins in the Declaration of Helsinki; and pertinent individual country/state/local laws and regulations. The study shall not begin until the required approval/favorable opinion from the Institutional Review Board/Human Research Ethics Committee (IRB/HREC) and/or regulatory authority has been obtained, if appropriate. See Section **10** below for additional information on study design and data collection.

The REPRISE IV study is registered at ClinicalTrials.gov (identifier NCT03618095).

7.2. *Treatment Assignment*

Screening materials from eligible subjects who are identified by the investigators as having met all the inclusion and none of the exclusion criteria (see below **Table 8.2-1** and **Table 8.3-1**, respectively) and who provide written informed consent will be reviewed by a Case Review Committee (CRC; see Section **21.2**) to assess and confirm suitability of subjects for enrollment. All subjects will have unique identification numbers.

Note 1: Subjects who have a bicuspid native valve will be enrolled in a separate nested registry cohort to assess safety and effectiveness. There will be a roll-in phase for centers that do not have previous experience implanting the LOTUS *Edge* Valve; each of these centers will perform at least 2 roll-in cases before commencing enrollment in the Main Cohort and Bicuspid Nested Registry cohort.

Note 2: A roll-in subject cannot have a bicuspid aortic valve.

7.2.1. Treatment

See Section **5** for a detailed description of the test device and information on device sizes.

The test device is the LOTUS *Edge* Valve System, which consists of a bioprosthetic bovine pericardial aortic valve and a delivery system. The large Lotus Introducer Set or, when available, the iSleeve Introducer Set (see Section **5.1.3**) is used as an accessory in the procedure. In countries where the introducer sets are approved, the commercial devices will be used. In countries where they are not approved, they will be considered investigational devices.

7.3. *Justification for the Study Design*

There will be up to 926 subjects in REPRISE IV. In order to support the stated objectives of this study (see Section **6.1**) while also limiting the potential exposure of study subjects to risk, up to 130 subjects will be enrolled in the roll-in phase of this study (at centers without previous LOTUS *Edge* valve experience), 696 subjects will be enrolled in the Main Cohort, and 100 subjects will be enrolled in the Bicuspid Nested Registry cohort. Up to 65 centers in the United States and Australia will participate in the study. Safety and effectiveness results will be reported on all enrolled subjects (see Section **19** for information on safety reporting). In addition to the risk-benefit analysis noted in Section **4.2** (see also Section **18**), ongoing dynamic data safety monitoring will be performed throughout the trial to minimize risk to subjects (see Section **21.1**). All implanted subjects will be followed for up to 10 years post index procedure. Per society guidelines[10,121] antiplatelet therapy with aspirin and/or a $P2Y_{12}$ inhibitor is recommended after TAVR to decrease the risk of thrombotic or thromboembolic complications if there are no contraindications to these medications.

8. Subject Selection

8.1. *Study Population and Eligibility*

The study will include subjects presenting with symptomatic severe aortic stenosis who are considered at intermediate risk for surgical valve replacement, including those who have a bicuspid native valve. Prior to being eligible for the REPRISE IV study, a subject must meet all of the inclusion criteria (Section **8.2**) and none of the exclusion criteria (Section **8.3**).

8.2. *Inclusion Criteria*

Subjects who meet all criteria in **Table 8.2-1** may be given consideration for inclusion in this clinical investigation, provided no exclusion criterion (see **Table 8.3-1**) is met.

Table 8.2-1: REPRISE IV Inclusion Criteria

IC1.	Subject has documented severe aortic stenosis defined as initial AVA ≤1.0 cm^2 (or AVA index of ≤0.6 cm^2/m^2) AND a mean pressure gradient ≥40 mm Hg OR maximal aortic valve velocity ≥4.0 m/s OR Doppler velocity index ≤0.25, as measured by echocardiography and/or invasive hemodynamics[a,b]. ***Note:*** In cases of low flow, low gradient aortic stenosis with left ventricular dysfunction (ejection fraction <50%), dobutamine can be used to assess the grade of aortic stenosis (maximum dobutamine dose of 20 mcg/kg/min recommended)[a]; the subject may be enrolled if echocardiographic criteria are met with this augmentation. a: Nishimura RA, et al. *J Am Coll Cardiol*. 2014;63:e57–185 b: Leon M, *et al. J Am Coll Cardiol.* 2011;57: 253–69
IC2.	A subject in the Bicuspid Aortic Valve Nested Registry cohort must have a documented Sievers Type 0 or Sievers Type 1 bicuspid aortic valve based on CT assessment and confirmed by the CT core lab with hemodynamic parameters that meet the criteria in IC1.
IC3.	Subject has a documented aortic annulus size of ≥20 mm and ≤27 mm based on the center's assessment of pre-procedure diagnostic imaging (and confirmed by the CRC).
IC4.	Subject has symptomatic aortic valve stenosis per IC1definition above with NYHA Functional Class ≥ II.
IC5.	Heart team (which must include an experienced cardiac interventionalist and an experienced cardiac surgeon) agrees that the subject is at intermediate risk of operative mortality (≥3% and <8% at 30 days based on the Society of Thoracic Surgeons [STS] risk score and other clinical comorbidities unmeasured by the risk calculator) and TAVR is appropriate. ***Note:*** Risk of operative mortality must be assessed via an in-person evaluation by a center cardiac surgeon and must be confirmed by the CRC (which must include an experienced cardiac surgeon).
IC6.	Heart team agrees that the subject is likely to benefit from valve replacement.
IC7.	Subject (or legal representative) has been informed of the study requirements and the treatment procedures and provides written informed consent.
IC8.	Subject, family member, and/or legal representative agree(s) and subject is capable of returning to the study hospital for all required scheduled follow up visits.
IC9.	Subject is expected to be able to take the protocol-required adjunctive pharmacologic therapy.

Table 8.2-1: REPRISE IV Inclusion Criteria

Abbreviations: AVA=aortic valve area; CRC=Case Review Committee; CT=computed tomography; NYHA=New York Heart Association; TAVR=transcatheter aortic valve replacement

8.3. *Exclusion Criteria*

Subjects who meet any one of the following criteria (**Table 8.3-1**) will be excluded from this clinical study.

Table 8.3-1: REPRISE IV Exclusion Criteria

EC1.	Subject has a unicuspid or bicuspid aortic valve (not applicable to subjects in the Bicuspid Nested Registry cohort). ***Note:*** Subjects in the Bicuspid Nested Registry cohort will have a documented Sievers Type 0 or Sievers Type 1 bicuspid aortic valve based on CT assessment and confirmed by the CT core lab. Subjects are not eligible for inclusion in the Bicuspid Nested Registry cohort if the maximum diameter of the ascending aorta is >45 mm or if the subject has another indication for aortic root replacement. Subjects with a Sievers Type 2 bicuspid valve are not eligible for enrollment in any study cohort.
EC2.	Subject has had an acute myocardial infarction within 30 days prior to the index procedure (defined as Q-wave MI or non–Q-wave MI with total CK elevation ≥ twice normal in the presence of CK-MB elevation and/or troponin elevation).
EC3.	Subject has had a cerebrovascular accident or transient ischemic attack clinically confirmed by a neurologist or neuroimaging within the past 6 months prior to study enrollment.
EC4.	Subject is on renal replacement therapy or has eGFR <20 (based on hospital preferred method). See AEC1 below if subject is in the CT Imaging Substudy.
EC5.	Subject has a pre-existing prosthetic aortic or mitral valve.
EC6.	Subject has severe (4+) aortic, tricuspid, or mitral regurgitation.
EC7.	Subject has moderate or severe mitral stenosis (mitral valve area ≤1.5 cm^2 and diastolic pressure half-time ≥150 ms, Stage C or D[121]).
EC8.	Subject has a need for emergency surgery for any reason.
EC9.	Subject has a history of endocarditis within 6 months of index procedure or evidence of an active systemic infection or sepsis.
EC10.	Subject has echocardiographic evidence of new intra-cardiac vegetation or intraventricular or paravalvular thrombus requiring intervention.
EC11.	Subject has platelet count <50,000 cells/mm^3 or >700,000 cells/mm^3, or white blood cell count <1,000 cells/mm^3.
EC12.	Subject will refuse transfusions or has had a gastrointestinal bleed requiring hospitalization or transfusion within the past 3 months or has other clinically significant bleeding diathesis or coagulopathy that would preclude treatment with required antiplatelet regimen.
EC13.	Subject has known hypersensitivity to contrast agents that cannot be adequately pre-medicated or has known hypersensitivity to aspirin, all $P2Y_{12}$ inhibitors, heparin, nickel, tantalum, titanium, or polyurethanes.

Table 8.3-1: REPRISE IV Exclusion Criteria

EC14.	Subject has a life expectancy of less than 24 months due to non-cardiac, comorbid conditions based on the assessment of the investigator at the time of enrollment.
EC15.	Subject has hypertrophic obstructive cardiomyopathy.
EC16.	Subject has any therapeutic invasive cardiac or vascular procedure within 30 days prior to the index procedure (except for balloon aortic valvuloplasty or pacemaker or implantable cardioverter defibrillator implantation, which are allowed).
EC17.	Subject has multivessel coronary artery disease with a Syntax score >22, and/or unprotected left main coronary artery.
EC18.	Subject has severe left ventricular dysfunction with ejection fraction <20%.
EC19.	Subject is in cardiogenic shock or has hemodynamic instability requiring inotropic support or mechanical support devices.
EC20.	Subject has arterial access that is not acceptable for the study device delivery systems as defined in the device Instructions For Use.
EC21.	Subject has severe vascular disease that would preclude safe access (e.g., aneurysm with thrombus that cannot be crossed safely; marked tortuosity; significant narrowing of the abdominal aorta; severe unfolding of the thoracic aorta; or thick, protruding, and/or ulcerated atheroma in the aortic arch).
EC22.	Subject has current problems with substance abuse (e.g., alcohol, etc.) that may interfere with the subject's participation in this study.
EC23.	Subject is participating in another investigational drug or device study that has not reached its primary endpoint.
EC24.	Subject has untreated conduction system disorder (e.g., Type II second degree atrioventricular block) that in the opinion of the treating physician is clinically significant and requires a pacemaker implantation. Enrollment is permissible after permanent pacemaker implantation.
EC25.	Subject has severe incapacitating dementia.
Additional exclusion criteria apply to subjects considered for enrollment in the CT Imaging Substudy as listed below:	
AEC1.	Subject has eGFR <30 mL/min (chronic kidney disease stage IV or stage V).
AEC2.	Subject has atrial fibrillation that cannot be rate controlled to ventricular response rate < 60 bpm.
AEC3.	Subject is expected to undergo chronic anticoagulation therapy after the index procedure. ***Note:*** Subjects treated with short-term anticoagulation post procedure can be included in the imaging substudy; in these subjects the 30-day imaging will be performed 30 days after discontinuation of anticoagulation.

Abbreviations: CK=creatine kinase; CT=computed tomography; MI=myocardial infarction

9. Subject Accountability

9.1. *Point of Enrollment*

Subjects who are confirmed eligible for the study by the CRC (see Section **21.2**) and who provided written informed consent are considered enrolled in the study as soon as an attempt is made to insert the LOTUS *Edge* Valve System into the subject's femoral artery.

9.2. *Discontinuation of Study Intervention*

If a LOTUS *Edge* valve test device is explanted during conventional scheduled or emergent surgical valve replacement or during an autopsy, if possible, the explanted valve should be assessed by the independent Histopathology Core Laboratory (Section **13.3.4**) for macroscopic and microscopic analyses. Please refer to the study Manual of Operations for recommendations on the explant procedure and shipment of the explanted valve.

Information on the explant procedure must be documented in source notes and captured in the Explant Form of the eCRFs.

9.3. *Withdrawal*

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

While all efforts will be made to minimize attrition, subjects may withdraw from the study at any time, with or without reason, and without prejudice to further treatment. Withdrawn subjects will not undergo any additional study follow-up, nor will they be replaced. The 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, unless local regulations apply. No new data will be collected after withdrawal.

All applicable case report forms up to the point of subject withdrawal and an "End of Study" form for the subject must be completed. If the withdrawal is due to investigator discretion, the investigator should follow-up with the subject per standard of care. Information on determining if a subject is lost to follow-up can be found in Section **9.4**.

9.4. *Lost to Follow-Up*

A subject will be considered "lost to follow-up" and terminated from the study when *all* of the following criteria have been met.

- Failure to complete 2 consecutive visits (or telephone follow-up as indicated in **Table 10.1-1**) without due cause (beginning with the 6-month and 1-year visits; i.e., subjects should not be considered lost to follow-up prior to the 1-year follow-up visit)
- Documentation of 3 unsuccessful attempts, one of which must be in written communication, by the Investigator or his/her designee to contact the subject or next of kin
- Notification from the Investigator to Sponsor reporting subject as lost to follow-up.

9.5. *End-of-Study Definition*

This clinical trial will be considered completed when subjects are no longer being examined or the last subject's last study visit as outlined in the data collection schedule (**Table 10.1-1**) has occurred. All subjects who receive a study device will be evaluated at discharge or 7 days (whichever comes first), 30 days, and annually up to 10 years post index procedure. Visits at 30 days, 1–5 years, 7 years and 10 years are office/in-person visits. Telephone follow-up is allowed at 6, 8, and 9 years. A subject's participation in the study will be considered complete after the 10-year visit. For subjects who do not receive a study device, participation in the study will be considered complete after the 1-year visit.

10. Study Methods

10.1. *Data Collection*

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

The study event schedule is shown diagrammatically in **Figure 10.1-1** and discussed in **Table 10.1-1** and Section **10.2** through Section **10.11**. The methods are based on VARC metrics[61,62], recommendations in the 2012 ACCF/AATS/SCAI/STS Expert Consensus Document on Transcatheter Aortic Valve Replacement[10] and the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease[121].

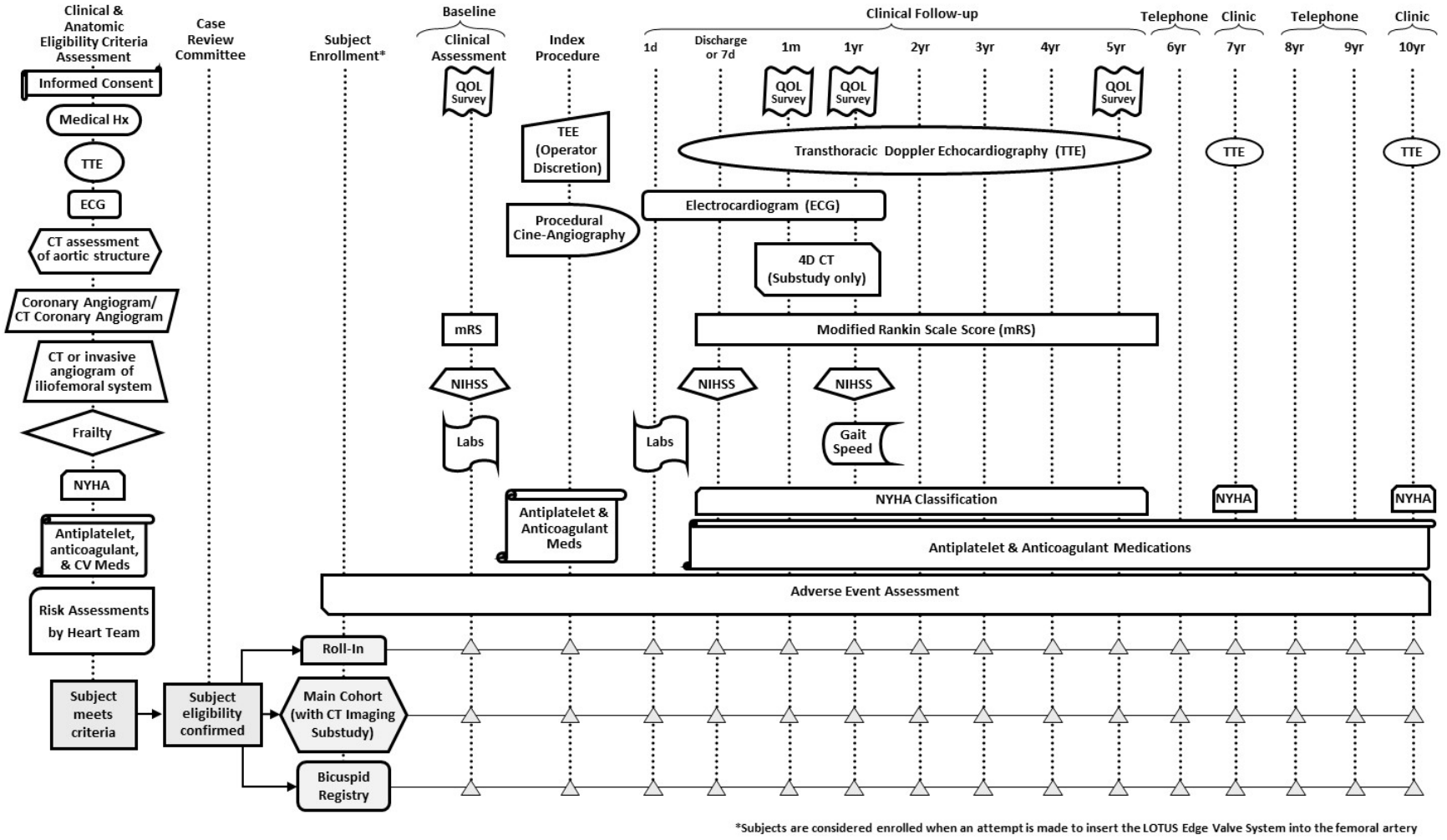


Figure 10.1-1: REPRISE IV Data Collection Scheme

Table 10.1-1: Study Event Schedule

Assessment	Screening[a]	Baseline	Procedure	Within 1 Day Post-procedure	Prior to Discharge or 7 Days Post-Procedure	30 Days[b] (±7 Days) Office Visit	12 Months[b] (±30 Days) Office Visit	24–60 Months[b] [Annual] (±45 Days) Office Visit	84 and 120 Months[b] (±60 Days) Office/In person Visit	72, 96, and 108 Months[b] (±60 Days) Telephone
Signed Informed Consent Form[c]	X	–	–	–	–	–	–	–	–	–
Demographics and medical history, including cardiac, neurological, renal (e.g., creatinine) and peripheral disease	X	–	–	–	–	–	–	–	–	–
NYHA Classification	X	–	–	–	X	X	X	X	X	–
NIHSS[d]	–	X	–	–	X	–	X	–	–	–
Modified Rankin Scale[d]	–	X	–	–	X	X	X	X	–	–
12-lead ECG[e]	X	–	–	X	X	X	X	–	–	–
Laboratory tests[f]	–	X	–	X	–	–	–	–	–	–
Risk assessments[g]	X	–	–	–	–	–	–	–	–	–
Frailty, disability and comorbidity[h]	X	–	–	–	–	–	X[h]	–	–	–
Antiplatelet and anticoagulant (if applicable) medications	X	–	X	–	X	X	X	X	X	X
Other CV medications	X	–	–	–	–	–	–	–	–	–
TTE[i]	X	–	–	–	X	X	X	X	X	–
TEE[j]	–	–	O	–	–	–	–	–	–	–
Coronary angiogram/CT coronary angiogram[k]	X	–	–	–	–	–	–	–	–	–
CT angiogram of aortic structure[l]	X	–	–	–	–	X[m]	–	–	–	–
CT angiogram of iliofemoral system[n]	X	–	–	–	–	–	–	–	–	–
QOL surveys[o]	–	X	–	–	–	X	X	X[p]	–	–

Table 10.1-1: Study Event Schedule

Assessment	Screening[a]	Baseline	Procedure	Within 1 Day Post-procedure	Prior to Discharge or 7 Days Post-Procedure	30 Days[b] (±7 Days) Office Visit	12 Months[b] (±30 Days) Office Visit	24–60 Months[b] [Annual] (±45 Days) Office Visit	84 and 120 Months[b] (±60 Days) Office/In person Visit	72, 96, and 108 Months[b] (±60 Days) Telephone
Procedural cine-angiography (including post-deployment aortogram)[q]	–	–	X	–	–	–	–	–	–	–
AE and ADE assessments[r]	–	–	X	X	X	X	X	–	–	–
Device deficiencies, SAE, SADE, UADE and CEC event assessments[s]	–	–	X	X	X	X	X	X	X	X
4D CT (Imaging Substudy only)[t]	–	–	–	–	–	X	X	–	–	–

Note 1: X = required; O = optional; – = not required; follow-up should be done by study personnel or as noted below.

a: Screening materials for CRC review should be submitted electronically at least 5 days in advance of CRC review.

b: All follow-up dates will be calculated from the date of the (attempted) index procedure. Where indicated, visits must be an office/clinical/in person visit but may be done in-hospital should the subject be admitted at the time. Subjects who are enrolled but do not receive a study device will be followed for 1 year to assess for safety but do not need to have protocol required TTE or ECG.

c: Study-specific consent includes screening consent to perform required assessments that will be evaluated by the CRC to confirm subject eligibility. If the study Informed Consent Form is modified during the course of the study, study subjects will be re-consented as necessary.
Note 2: The subject should undergo the index procedure within 30 days after signing the study Informed Consent Form.

d: NIHSS and mRS must be performed by a neurology professional or certified personnel (external certification for NIHSS; internal or external certification for mRS). The NIHSS and mRS assessors should be independent (not involved with the care of study subjects). For subjects diagnosed with a stroke, a neurological physical exam, mRS, and NIHSS must be performed after the event; mRS must also be administered at 90±14 days after a stroke; the simplified mRS questionnaire may be used for this follow-up assessment. The neurological physical examination must be performed by a neurologist, neurology fellow, neurology physician assistant, or neurology nurse practitioner who is independent of the study. If a subject who has not received a study device experiences a stroke within the first 1 year after the index procedure, mRS must be performed on that subject after the event; mRS must also be administered at 90±14 days after a stroke and the results must be reported to the Sponsor.

e: All screening and post-procedure 12-lead ECGs must be performed according to the ECG Core Laboratory guidelines (see study Manual of Operations). If the subject is enrolled, the ECG must be provided to the Core Laboratory.

f: Laboratory tests at baseline include CBC with platelets, albumin, serum creatinine, and cardiac enzymes. Cardiac enzymes (CK is required, CK-MB or troponin if CK is elevated) must be collected twice at intervals per standard of care within 6-24 hours post-procedure. Acute kidney injury (AKI) should be assessed through discharge/7 days based on the AKIN system.

Table 10.1-1: Study Event Schedule

Assessment	Screening[a]	Baseline	Procedure	Within 1 Day Post-procedure	Prior to Discharge or 7 Days Post-Procedure	30 Days[b] (±7 Days) Office Visit	12 Months[b] (±30 Days) Office Visit	24–60 Months[b] [Annual] (±45 Days) Office Visit	84 and 120 Months[b] (±60 Days) Office/In person Visit	72, 96, and 108 Months[b] (±60 Days) Telephone

g: Consists of STS score, euroSCORE II, and heart team assessment including an in-person evaluation by a center cardiac surgeon that must be confirmed by the CRC (which must include an experienced cardiac surgeon).

h: Frailty, disability, and comorbidity risk assessments must be captured at screening: height, weight, strength and balance (use of wheelchair, gait speed to walk 5 meters, number of falls in the past 6 months, maximal grip strength), and activities of daily living (Katz Index); at 1 year, gait speed to walk 5 meters must be assessed again.

i: Transthoracic echocardiogram (TTE) is required for all subjects who have a study valve implanted in the aortic position. This includes assessment of EOA, peak and mean aortic valve pressure gradients, peak aortic velocity, aortic regurgitation assessment, and LVEF. Screening TTE must be performed within 60 days prior to CRC approval. At least 1 echocardiogram must be obtained before discharge or 7 days (whichever comes first); if multiple echocardiographic studies are performed prior to discharge and within 7 days of the procedure, the latest study performed will be used for analysis. All TTEs must be performed according to the Echocardiography Core Laboratory procedure guidelines (see study Manual of Operations). If a subject does not receive an implanted study valve, then no follow-up TTE is required.
Note 3: In cases of low flow low gradient aortic stenosis with left ventricular dysfunction (ejection fraction <50%), dobutamine can be used to assess the grade of aortic stenosis; the subject may be enrolled if echocardiographic criteria are met with this augmentation. In cases where a subject who has met the echocardiographic criteria for enrollment receives BAV prior to the index procedure and subsequently no longer meets the REPRISE IV aortic valve pressure gradient or EOA criteria, the subject may still be enrolled based on the pre-BAV echocardiographic data. In such cases, the most recent echocardiogram done prior to the index procedure (even if after BAV) must be submitted to the Echocardiography Core Laboratory to be included in the baseline data.

j: TEE can be performed at the discretion of the operator.

k: A coronary angiogram/CT coronary angiogram must be performed within 365 days prior to CRC approval. If there is concern regarding the current extent of coronary artery disease or aortic stenosis, the CRC may recommend a repeat study closer to the time of enrollment.

l: A CT angiogram of the aortic complex must be performed within 180 days prior to CRC approval (and should be performed within 90 days if possible) to evaluate the aortic valve anatomy and aortic root dimensions for device sizing. CT angiogram must be performed according to the CT/X-ray Core Laboratory procedure guidelines (see study Manual of Operations). It must be sent to the Core Laboratory for detailed measurements and analyses in advance of the CRC review where results will be assessed to confirm subject's eligibility.

m: For subjects in the Bicuspid Nested Registry Cohort, a computed tomography scan at 30 days post LOTUS *Edge* valve implantation. Please refer to the CT Core Laboratory procedure guidelines (see study Manual of Operations). Results must be sent to the CT Core Laboratory.

n: An assessment of the iliofemoral system must be performed within 180 days prior to CRC approval (and should be performed within 90 days if possible). A CT angiogram of the iliofemoral system should be performed for complete visualization of the iliac and femoral arteries to assess for dimensions, tortuosity, and calcification. The CT angiogram should be performed per the procedure guidelines (see study Manual of Operations) and sent to the CT

Table 10.1-1: Study Event Schedule

Assessment	Screening[a]	Baseline	Procedure	Within 1 Day Post-procedure	Prior to Discharge or 7 Days Post-Procedure	30 Days[b] (±7 Days) Office Visit	12 Months[b] (±30 Days) Office Visit	24–60 Months[b] [Annual] (±45 Days) Office Visit	84 and 120 Months[b] (±60 Days) Office/In person Visit	72, 96, and 108 Months[b] (±60 Days) Telephone

Core Laboratory with the screening CT angiogram of the aortic structure. An iliofemoral invasive angiogram may be substituted for the iliofemoral CT angiogram.

o: Includes the Kansas City Cardiomyopathy and SF-12 QOL questionnaires. Baseline QOLs should be performed within 30 days prior to the index procedure.

p: QOL survey at 60 months.

q: Procedural cine-angiogram including the baseline images of the aortic complex and the final post-deployment aortogram of the ascending aorta must be performed and sent to the CT/X-Ray Core Laboratory for analysis.

r: AEs and ADEs will be monitored and collected from the time of enrollment through 12-month follow-up. For subjects who do not receive the study device, AEs will be monitored through 12-month follow-up.

s: Information on device deficiencies for the test device(s) will be monitored and reported to Boston Scientific. Information on all SAEs, SADEs, UADEs, and CEC events will be monitored and reported to Boston Scientific for enrolled subjects from the time of enrollment through 5 years. After 5 years, serious adverse event assessment (includes SAE, SADE, UADE, and relevant VARC events to be adjudicated by the CEC [see ***Note 4*** below]) for test device(s) and device deficiencies assessment for test device(s) with associated treatment will be monitored and reported to Boston Scientific for enrolled subjects through termination of the study. For subjects who do not receive a study device, the aforementioned events will be monitored through 1-year post-index procedure. Please refer to Section 6.2.2 for a list of CEC events and Table 25.2-1 for definitions of these events, which specify data required for CEC adjudication. Complaint reporting of any device deficiencies for any commercially available products used should be carried out using the manufacturer's processes.

Note 4: Relevant VARC events after 5 years to be adjudicated by the CEC include the following: mortality, stroke, spontaneous myocardial infarction, acute kidney injury, repeat procedure for valve-related dysfunction, hospitalization for valve-related symptoms or worsening congestive heart failure (NYHA III or IV), new pacemaker, new onset atrial fibrillation or atrial flutter, prosthetic aortic valve malpositioning (valve migration, valve embolization, or ectopic valve deployment), TAV-in-TAV, prosthetic aortic valve thrombosis and endocarditis.

t: For subjects in the CT Imaging Substudy, a 4D CT scan at 30 days and at 1-year post LOTUS *Edge* valve implantation must be done. Please refer to the CT Core Laboratory procedure guidelines (see study Manual of Operations). The data must be sent to the independent CT core laboratory.

Table 10.1-1: Study Event Schedule

Assessment	Screening[a]	Baseline	Procedure	Within 1 Day Post-procedure	Prior to Discharge or 7 Days Post-Procedure	30 Days[b] (±7 Days) Office Visit	12 Months[b] (±30 Days) Office Visit	24–60 Months[b] [Annual] (±45 Days) Office Visit	84 and 120 Months[b] (±60 Days) Office/In person Visit	72, 96, and 108 Months[b] (±60 Days) Telephone

Abbreviations: AE=adverse event; ADE=adverse device effect; AKI=acute kidney injury; BAV=balloon aortic valvuloplasty; CBC=complete blood count; CEC=Clinical Events Committee; CK-MB=creatine kinase-myoglobin band; CRC=Case Review Committee; CT=computed tomography; CV=cardiovascular; ECG=electrocardiogram; EOA= effective orifice area; LDH=lactate dehydrogenase; LV=left ventricle; MRI=magnetic resonance imaging; mRS=modified Rankin Scale; NIHSS=National Institutes of Health Stroke Scale; NYHA=New York Heart Association; QOL=Quality of Life; SAE=serious adverse event; SADE=serious adverse device effect; STS=Society of Thoracic Surgery; TEE=transesophageal Doppler echocardiography; TTE=transthoracic Doppler echocardiography; UADE=unanticipated adverse device effect; VARC=Valve Academic Research Consortium

10.2. *Study Candidate Screening*

Subjects will be evaluated for eligibility by the center heart team (which must include an experienced cardiac interventionalist and an experienced cardiac surgeon). The heart team should take into account the Society of Thoracic Surgeons (STS) score as well as other clinical comorbidities (including frailty) not accounted for in the risk calculation. Eligible subjects will have agreement from the heart team that the subject is at intermediate operative risk of mortality with SAVR (see **Table 8.2-1** for inclusion criteria). Risk of operative mortality and morbidity is to be assessed via an in-person evaluation by a center cardiac surgeon and must be confirmed by the CRC (which must include an experienced cardiac surgeon). The heart team must also agree that the subject is likely to benefit from valve replacement.

Clinical assessment and evaluation, collected tests and images (e.g., echocardiography, computerized tomography [CT], angiography) performed in preparation for TAVR, and any planned use of balloon aortic valvuloplasty (BAV) will be reviewed by the CRC (see Section **7.2** and Section **21.2**). The CRC will be comprised of experienced cardiac surgeons, interventional cardiologists, and Sponsor staff proficient with the LOTUS *Edge* Valve System and will confirm subject eligibility for enrollment.

10.2.1. Strategies for Recruitment and Retention

The REPRISE IV study will include subjects presenting with documented severe native aortic valve stenosis who are indicated for TAVR (see Section **8**). It is estimated that nearly 5% of elderly ≥75 years of age have aortic stenosis and its prevalence is expected to increase due to an aging population[2,3]. Because aortic stenosis most commonly occurs in the very elderly, women are well represented in TAVR trials. Traditionally underrepresented populations (elderly and women) are expected to be included in the subject population as allowed by governing law/national regulation; as the very elderly will represent the majority of subjects enrolled in the trial, efforts to maximize retention are by definition targeted to traditionally under-represented groups. The inclusion and exclusion criteria are not expected to have a negative effect on recruitment or retention of said populations. In the United States, the subjects eligible for inclusion in this study are likely to be Medicare patients due to their expected age and the results of this study are likely to be highly generalizable to a Medicare population.

All efforts will be made to minimize attrition in REPRISE IV (see Section **9.4**). Investigators are encouraged to enroll subjects who are willing to comply with the follow-up requirements of the study. If a visit is missed, the center should attempt to contact the subject to reschedule the missed visit and counsel the subject on the importance of maintaining the assigned visit schedule.

10.3. *Subject Informed Consent*

Informed consent (see Section **20**) must be obtained from a potential subject prior to conducting any preoperative assessments that are not part of the local routine preparation and evaluation of a subject for TAVR, even if the subject's eligibility has not yet been completely determined.

The Investigator/designee, who has been trained on the protocol, will explain the nature and scope of the study, potential risks and benefits of participation, and answer questions for the subject. If the subject agrees to participate, the IRB/HREC-approved ICF must be signed and personally dated by the subject or his/her legally authorized representative. The Investigator/designee must also sign the ICF prior to subject enrollment. Any additional persons required by the center's IRB/HREC to sign the ICF must also comply. Study personnel should explain to the subject that even if the subject agrees to participate in the study and signs the ICF, the heart team and/or the CRC may determine that the subject is not a suitable candidate for the study and/or TAVR procedure.

If during the course of the preoperative evaluations, the subject is found not to be eligible for inclusion in the study, the subject should be notified. Reason for ineligibility will be accounted for as "screening failure" and will be documented as such in the eCRF screening module. If the subject has signed the ICF but is found not eligible for inclusion in the study prior to or during the procedure, the subject should receive the appropriate treatment as identified by the clinical investigator. Information regarding the screening failure will be captured on the screening module and subject will be included in the "screening cohort" accountability.

10.4. *Screening Assessments*

Results from the screening tests and procedures listed below must be submitted to the CRC (see Section **21.2**) for evaluation to confirm a subject's eligibility for the study. Screening assessment documentation should be provided via electronic upload at least 5 days in advance of a scheduled CRC review or at least 5 days in advance of the planned procedure date. It is planned that CRC reviews will take place at least weekly or as needed to ensure timely review and confirmation of subject eligibility.

Note 1: It is recommended that predilatation be performed unless there is minimal calcification of the annulus and leaflets. Subjects in the bicuspid registry must have predilatation performed.

Note 2: Additional concomitant procedures, including percutaneous coronary intervention, are not allowed during the index procedure.

Centers will be trained on the screening process (see Section **16.4.2**). Specific data points will be collected in the REPRISE IV electronic case report forms (eCRFs) as shown below.

- Clinical assessments
    - Demographics including age and gender

- Medical history (general medical; cardiac [including previous cardiac surgery]; neurological, renal [including creatinine] and peripheral disease; and other medical conditions)
- Physical examination including weight and height
- NYHA classification
- Current antiplatelet and other cardiovascular medications
- 12-lead electrocardiogram (ECG) at screening must be performed according to the ECG Core Laboratory guidelines (see study Manual of Operations) and, if subject is enrolled, forwarded to the core laboratory for analysis
- Risk assessments: Society of Thoracic Surgeons (STS) score, euroSCORE II, heart team assessment including an in-person evaluation by a center cardiac surgeon and any frailty assessments (detailed in next bullet).

- Frailty, disability, and comorbidity assessments (collected prospectively)[122,123]
  - Body Mass Index from the physical exam
  - Strength and balance
    - Use of wheelchair
    - Gait speed as measured by a stopwatch for a subject to walk 5 meters (3 measures averaged)[123-125]
    - Number of falls in the past 6 months
    - Maximal grip strength (kg) in the dominant hand (3 measures averaged), using a hand-held dynamometer[126]
  - Activities of daily living: Katz Index[122,127] is based on an evaluation of the functional independence or dependence of a subject in bathing, dressing, going to toilet, transferring, continence, and feeding. A point is assigned for independence in each of the 6 functions, and 0 points if there is any dependence in these 6 categories.

- Imaging assessments
  - Within 60 days prior to CRC approval, TTE (2-D, M-Mode, and color) must be carried out. The evaluation should include assessment of effective orifice area (EOA), peak and mean aortic valve gradient pressure, aortic regurgitation assessment, mitral regurgitation, LVEF, left ventricular end-diastolic and end-systolic diameter, tricuspid regurgitation (TR) jet velocity, and left atrial (LA) volume. The TTE must be performed according to the Echocardiography Core Laboratory procedure guidelines (see study Manual of Operations). For enrolled subjects, the TTE must be provided to the echocardiography core laboratory for independent analyses. In cases of low flow/low gradient aortic stenosis with left ventricular dysfunction (ejection fraction <50%), dobutamine can be used to assess the grade of aortic stenosis (maximum dobutamine dose of 20 mcg/kg/min recommended)[121]; the subject may be enrolled if echocardiographic criteria are met with this augmentation. In cases where a subject who has met the echocardiographic

criteria for enrollment receives BAV prior to the index procedure and subsequently no longer meets the REPRISE IV aortic valve pressure gradient or EOA criteria, the subject may still be enrolled based on the pre-BAV echocardiographic data. In such cases, the most recent echocardiogram done prior to the index procedure (even if after BAV) must be submitted to the Echocardiography Core Laboratory to be included in the baseline data.

- A coronary angiogram/CT coronary angiogram must be performed within 365 days prior to CRC approval. If there is concern regarding the current extent of coronary artery disease or aortic stenosis, the CRC may recommend a repeat study closer to the time of enrollment. An aortogram and hemodynamics including simultaneous ascending aorta and left ventricle pressure measurements should be performed.
- A CT angiogram of the aortic complex must be performed 180 days prior to CRC approval (and should be performed within 90 days if possible) to evaluate the aortic valve anatomy and aortic root dimensions to determine eligibility and device sizing. It must meet the CT Core Laboratory procedure guidelines (see study Manual of Operations) and be provided in advance to the core laboratory for detailed measurements and independent analyses, which will be reviewed by the CRC to confirm a subject's eligibility.
- An assessment of the iliofemoral system must be performed within 180 days prior to CRC approval (and should be performed within 90 days if possible). A CT angiogram of the iliofemoral system should be performed for complete visualization of the iliac and femoral arteries to assess for dimensions, tortuosity, and calcification. The CT angiogram of the iliofemoral system should be performed per the procedure guidelines (see study Manual of Operations) and provided to the CT Core Laboratory with the screening CT angiogram of the aortic structure for independent measurements and review by the CRC to confirm a subject's eligibility. An iliofemoral invasive angiogram may be substituted for the iliofemoral CT angiogram.

10.5. *Baseline Assessments*

The following assessments must be completed within 30 days prior to the index procedure, unless otherwise specified below. The REPRISE IV eCRFs identify the specific data points to be collected.

- Confirmation of CRC approval date
- NIH Stroke Scale (NIHSS), which must be performed by a neurology professional or certified personnel (external certification); NIHSS assessors should be independent (not involved with the care of study subjects)
- Modified Rankin Scale (mRS) score, which must be performed by a neurology professional or certified personnel (external or internal certification); mRS assessors should be independent (not involved with the care of study subjects)

- Laboratory tests
  - Complete blood count (CBC) with platelets
  - Albumin
  - Serum creatinine
  - Cardiac enzymes (creatine kinase [CK] is required, CKMB or troponin if CK is elevated)
- Quality Of Life (QOL) Surveys: Kansas City Cardiomyopathy[118] and SF-12[119] QOL Questionnaires

Note: In cases where a subject who has met the echocardiographic criteria for enrollment receives BAV prior to the index procedure and subsequently no longer meets the REPRISE IV aortic valve pressure gradient or EOA criteria, the subject may still be enrolled based on the pre-BAV echocardiographic data. In such cases, the most recent echocardiogram done prior to the index procedure (even if after BAV) must be submitted to the Echocardiography Core Laboratory to be included in the baseline data.

10.6. *Pre-procedure Medications*

- Antiplatelet Therapy:

  Per society guidelines[10,121] antiplatelet therapy is recommended to reduce the risk of thrombotic or thromboembolic complications if there are no contraindications to these medications. Study subjects must receive some antiplatelet therapy (aspirin and/or a $P2Y_{12}$ inhibitor) for at least 1 month following valve implant. A loading dose of the same antiplatelet medication (aspirin and/or a $P2Y_{12}$ inhibitor) is required for subjects who have not been on the antiplatelet therapy for ≥72 hours at the time of the index procedure (see below for recommended doses).

  Aspirin Dose

  The recommended loading dose of aspirin is 75–325 mg for subjects who have not been on aspirin therapy for ≥72 hours at the time of the index procedure. The loading dose must be administered prior to the implant procedure. Subjects who have been taking aspirin daily for ≥72 hours at the time of the index procedure do not require a loading dose of aspirin.

  $P2Y_{12}$ Inhibitor Dose (Clopidogrel Recommended)

  The recommended loading dose of a $P2Y_{12}$ inhibitor is ≥300 mg clopidogrel, 60 mg prasugrel, or 180 mg ticagrelor for subjects who have not been on $P2Y_{12}$ inhibitor therapy for ≥72 hours at the time of the index procedure. The loading dose must be administered prior to the implant procedure. Subjects who have been taking a $P2Y_{12}$

inhibitor daily for ≥72 hours at the time of the index procedure do not require a loading dose of the $P2Y_{12}$ inhibitor.

Note: If a subject is treated with anticoagulation, either a $P2Y_{12}$ inhibitor or aspirin is recommended prior to the implant procedure (but both aspirin and a $P2Y_{12}$ inhibitor are not recommended).

- Anticoagulant therapy (e.g., unfractionated heparin) must be administered per local standard of care during the implant procedure, with a recommended target activated clotting time (ACT) of ≥250 seconds during the implantation procedure.
- Additionally, the subject should be given prophylactic antibiotic therapy according to local practice. The choice of antibiotic drug is left to the investigator's discretion.

10.7. *Index Procedure*

The preparation of the subject for the percutaneous procedure will be performed following standard techniques. Transfemoral access must be attempted for all subjects (assessment of the iliofemoral system prior to subject enrollment must indicate that transfemoral access is considered appropriate). If the transfemoral approach is unsuccessful, the operator will decide the best alternative approach to treat the subject.

Note 1: Additional concomitant procedures, including percutaneous coronary intervention, are not allowed during the index procedure.

Note 2: The subject should undergo the index procedure within 30 days after signing the study Informed Consent Form.

The large Lotus Introducer Set (Section **5.1.3**) or, when available, the iSleeve Introducer Set (Section **5.1.3**) is prepared and introduced in the patient's femoral artery, as described in the iSleeve/Lotus Introducer IFUs. A balloon valvuloplasty on the existing valve following standard techniques may be performed with an appropriately sized valvuloplasty balloon (avoid oversizing) before implantation of the LOTUS *Edge* valve. Careful attention should be paid to the position of the guidewire throughout the BAV procedure. Prior to introduction of the LOTUS *Edge* Valve System, the subject's hemodynamic status and heart rhythm must be assessed and documented (12-lead ECG is not required). Information on the BAV, including number of inflations, should be documented in the source data and will be captured in the eCRFs.

Note 3: It is recommended that predilatation be performed unless there is minimal calcification of the annulus and leaflets; BAV must be performed in subjects in the Bicuspid Nested Registry cohort.

Note 4: If the subject becomes hemodynamically unstable after the valvuloplasty for reasons unrelated to the aortic valve annulus and/or leaflets, the LOTUS *Edge* valve implantation should be interrupted until the subject is stable.

The LOTUS *Edge* valve implantation procedure requires two operators: First and Second Operators. Both operators must comply with the IFU and must be adequately trained and

certified by BSC personnel before performing the procedure (see Section 16.4.2**16.4.2** for additional information on training). Guidelines provided by the Sponsor for valve size selection should be followed.

The LOTUS *Edge* Valve System must be prepared in accordance with the IFU. Device preparation should only be performed by persons who have completed appropriate training with the LOTUS *Edge* Valve System.

Prior to insertion of the LOTUS *Edge* Valve System catheter into the iSleeve/Lotus Introducer, the recommended target ACT of ≥250 seconds should be confirmed, with additional boluses of heparin administered if needed.

The LOTUS *Edge* Valve System IFU should be followed. The following summarizes the LOTUS *Edge* Valve System procedure.

1) The LOTUS *Edge* delivery catheter is back-loaded onto a 0.035 in (0.89 mm) Super/Extra Stiff guidewire, maintaining proper guidewire positioning across the existing valve and into the ventricle.
2) The LOTUS *Edge* catheter is inserted in the iSleeve/Lotus Introducer and carefully advanced through the aorta and the aortic arch under fluoroscopy.
3) The catheter is then advanced slowly through the aortic annulus. The valve is then mechanically expanded and locked into the desired position.
4) Prior to the release of the LOTUS *Edge* valve, assessment of its position and function is performed using contrast injection and/or TEE.
5) If the position of the valve is deemed too aortic or too ventricular, the valve is then partially or completely resheathed inside the catheter, with a repositioning made by either pulling or pushing the catheter carefully, using the frame as a guide. The valve can then be re-expanded.
6) Once the LOTUS *Edge* valve position is deemed satisfactory and the valve is fully locked, the release process is then initiated, and the LOTUS *Edge* valve is detached from the catheter.
7) The nosecone is recaptured, and the system pulled out of the body.
8) A final post-deployment aortogram of the ascending aorta must be performed and forwarded to the core laboratory with the procedural cine-angiogram for analysis.
9) The iSleeve/Lotus Introducer is then removed.
10) The femoral access is then closed according to standard practice.

Labels from the devices used during the procedure (e.g., the LOTUS *Edge* Valve System, iSleeve, Lotus Introducer) should be retained so that they can be included in the appropriate source documents and reported in the eCRFs.

During the procedure, designated center study personnel must capture necessary information on acute device/delivery system performance and procedure. The following information will be collected during the procedure.

- Date of procedure
- Device size (23mm, 25mm, or 27mm) and model
- Time of puncture (at site of TAVR sheath) and time of vascular closure for TAVR sheath (iSleeve/Lotus Introducer insertion and removal time)
- Descriptive information on balloon valvuloplasty, if performed (e.g., size of balloon, number of balloon inflations)
- Adjunctive procedures performed during implant procedure
- LOTUS *Edge* Valve System catheter insertion and removal time
- Descriptive information on LOTUS *Edge* valve implantation procedure and information on valve repositioning or retrieval (if performed)
- Adverse event (AE) assessment and associated treatment (including AE, serious adverse event [SAE], serious adverse device effect [SADE], unanticipated adverse device effect [UADE], adverse device effect [ADE] and Clinical Events Committee [CEC] events; see Section **19**).
- Device deficiencies assessment for the LOTUS *Edge* Valve System

Note 5: All LOTUS *Edge* valve implantation procedures will be performed with the support/presence of trained BSC personnel (see Section **16.4.1**).

Note 6: In countries where the introducer sets are approved, a device deficiency should be reported as a complaint.

10.8. *Post Index Procedure*

The following are to be performed post-procedure.

- Per society guidelines[10,121] antiplatelet therapy with aspirin and/or a $P2Y_{12}$ inhibitor (clopidogrel recommended) is recommended to reduce the risk of thrombotic or thromboembolic complications if there are no contraindications to these medications. Study subjects must receive some antiplatelet therapy (aspirin and/or a $P2Y_{12}$ inhibitor) for at least 1 month following valve implantation. It is recommended that subjects be treated with both aspirin and a $P2Y_{12}$ inhibitor for at least 1 month. Extended dual antiplatelet therapy may be administered per physician choice.
    - After the valve implant procedure, aspirin (recommended dose of ≥75 mg daily) should be given for at least 1 month. It is recommended that daily aspirin be given indefinitely thereafter as per local standard of care. Aspirin dose may be adjusted to the closest approximation based on local tablet formulation availability.
    - After the valve implant procedure, a $P2Y_{12}$ inhibitor is recommended for at least 1 month. Dosing should follow local standard of care.
    - If a subject is treated with chronic anticoagulation, either a $P2Y_{12}$ inhibitor or aspirin is recommended after the implant procedure in addition to the anticoagulant

therapy (but both aspirin and a $P2Y_{12}$ inhibitor are not recommended). The subject should be treated with an oral anticoagulant (OAC) and either a $P2Y_{12}$ inhibitor (clopidogrel recommended) or aspirin for at least 1 month.

- Prophylactic antibiotic regimen should be completed as per local practice.
- Additional medications may be used at the investigator's discretion.
- It is recommended that the subject's heart rhythm be monitored using telemetry for at least 48 hours after the index procedure.
- 12-lead ECG must be completed within 24 hours post-procedure per the ECG core laboratory guidelines (see study Manual of Operations) and must be forwarded to the core laboratory for analysis.
- Cardiac enzymes (CK is required, CK-MB or troponin if CK is elevated) must be collected twice within 6 to 24 hours post-procedure at intervals per local standard of care.

10.9. *Prior to Discharge or 7 Days Post-Procedure (Whichever Comes First)*

Subjects must be evaluated prior to discharge or 7 days post-procedure (whichever comes first) based on the assessments below. The REPRISE IV eCRFs identify the specific data points to be collected.

- NYHA classification
- NIHSS, which must be performed by a neurology professional or certified personnel (external certification); NIHSS assessors should be independent (not involved with the care of study subjects).
- Modified Rankin Scale score, which must be performed by a neurology professional or certified personnel (external or internal certification); mRS assessors should be independent (not involved with the care of study subjects).
- 12-lead ECG per the ECG Core Laboratory guidelines (see study Manual of Operations) and must be forwarded to the core laboratory for analysis.
- TTE, including assessment of EOA, peak 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 the Echocardiography Core Laboratory procedure guidelines (see study Manual of Operations). All TTEs for enrolled subjects must be provided to the Echocardiography Core Laboratory for independent analyses.

  Note: For all subjects who have a transcatheter valve implanted in the aortic position during the index procedure at least 1 echocardiogram must be obtained before discharge or 7 days (whichever comes first); if multiple echocardiographic studies are performed prior to discharge and within 7 days of the procedure, the latest study

performed will be used for analysis. Subjects who do not receive a transcatheter valve during the index procedure are not required to have follow-up TTE.

- Current antiplatelet and anticoagulant (if applicable) medications
- Complete adverse event (AE, SAE, SADE, UADE, ADE, and CEC events) assessment for test device(s) and device deficiencies assessment for test device(s), with associated treatment.

10.10. *Follow-up*

All implanted subjects will be evaluated at 30 days and then annually up to 10 years post index procedure. Subjects who do not have a study device implanted will be assessed through 1 year post index procedure for safety/adverse events. Physical clinic visits or in-person follow-up visits are scheduled for appointed times after the date of the procedure through 5 years and at 7 and 10 years. Telephone follow-up is allowed at 6, 8, and 9 years. It is important that this schedule be maintained as closely as possible for all subjects. Boston Scientific Corporation 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 is allowed is indicated in **Table 10.1-1**. Visits/telephone follow-up not completed will be considered missed and recorded as protocol deviations. Visits/telephone follow-up completed outside these windows will be recorded as protocol deviations. Boston Scientific or its designee will review protocol deviations on a regular basis in accordance with applicable standard operating procedures.

Each follow-up must be performed as noted in **Table 10.1-1**. Data from the required tests and images as well as medical assessments will be recorded in source documentation and captured in the eCRFs. The determination of specified study endpoints and measurements such as valve function and CEC events will require data from images and tests as outlined in the event definitions in **Table 25.2-1**.

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.

Note 1: The follow-up visits at 30 days, 1–5 years, 7 years, and 10 years must be conducted in-person. If an in-person assessment cannot be performed, follow-up by telephone should be attempted. Subject or subject's physician should provide rationale for why the in-person assessment cannot be performed.

Note 2: A subject who has received a study valve should not be enrolled in a clinical trial of an investigational drug/device/treatment until the subject has reached the REPRISE IV primary endpoint (1 year).

10.10.1. 30-Day Follow-up (30±7 Days)

All enrolled subjects must be evaluated in person 30 (±7) days after the index procedure. During the 30-day follow-up visit, the following assessments must be completed. The REPRISE IV eCRFs identify the specific data points to be collected.

- NYHA classification
- Modified Rankin Scale score, which must be performed by a neurology professional or certified personnel (external or internal certification); mRS assessors should be independent (not involved with the care of study subjects).
- 12-lead ECG per the ECG Core Laboratory guidelines (see study Manual of Operations), which must be forwarded to the core laboratory for analysis.
- Current antiplatelet, anticoagulant (if applicable) medications
- TTE including assessment of EOA, peak 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. TTE must be performed per the Echocardiography Core Laboratory procedure guidelines (see study Manual of Operations). All TTEs for enrolled subjects must be provided to the Echocardiography Core Laboratory for independent analyses.

  Note: TTE must be done for all subjects who have a transcatheter valve implanted in the aortic position during the index procedure. Subjects who do not receive a transcatheter valve during the index procedure are not required to have follow-up TTE.
- Quality of Life Surveys: Kansas City Cardiomyopathy and SF-12 Quality of Life Questionnaires

  Note: Quality of life will be evaluated by the Kansas City Cardiomyopathy[118] and SF-12[119] questionnaires at baseline, 1 month, 1 year, and 5 years. A formal health economics analysis may be completed if meaningful clinical results are obtained.
- Complete adverse event (AE, SAE, SADE, UADE, ADE and CEC events) assessment for test device(s) and device deficiencies assessment for test device(s), with associated treatment
- For subjects in the Bicuspid Nested Registry cohort, a computed tomography scan at 30 days post LOTUS *Edge* valve implantation. The CT scan must be performed per the CT Core Laboratory procedure guidelines (see study Manual of Operations) and sent to the CT Core Laboratory for independent analyses.
- For subjects in the CT Imaging Substudy, assessment of prosthetic valve leaflet mobility using 4D CT must be performed per the CT Core Laboratory procedure guidelines (see study Manual of Operations). All 4D CT scans for subjects enrolled in the CT Imaging Substudy must be sent to the CT Core Laboratory for independent analyses.

Note: The CT scans will be read by the CT Core Laboratory and will not be provided to local investigators except as per below. Local reading should be done only for non-cardiac valve findings such as unexpected lung pathology. A study CT scan can be unblinded upon investigator request based on any of the following if the event occurs within 2 weeks of the study CT scan.

- Any neurological event
- Any potential embolic event
- Any MI (ST segment elevation MI or non-ST segment elevation MI)
- Increase in aortic regurgitation to moderate or severe
- A change in echocardiographic parameters including an increase in mean gradient of >10 mmHg or a change in Doppler velocity index (DVI) of >0.05.

If any of the above events occurs outside of the 2-week window around the study CT scan, the investigator must not be unblinded to the core laboratory assessment of the study CT scan and instead should perform a separate CT scan if clinically indicated. If an additional CT scan is performed for clinical indications, it should be sent to the CT Core Laboratory for analysis.

10.10.2. 12-Month Follow-up (365±30 Days)

All implanted subjects must be evaluated in person 365 (±30) days after the index procedure. During the 12-month follow-up, the following assessments must be completed. The REPRISE IV eCRFs identify the specific data points to be collected.

- Weight and height
- NYHA classification
- Modified Rankin Scale score, which must be performed by a neurology professional or certified personnel (external or internal certification); mRS assessors should be independent (not involved with the care of study subjects).
- NIHSS, which must be performed by a neurology professional or certified personnel (external certification); NIHSS assessors should be independent (not involved with the care of study subjects).
- Gait speed to walk 5 meters
- 12-lead ECG per the ECG Core Laboratory guidelines (see study Manual of Operations) and must be forwarded for analysis
- Current antiplatelet and anticoagulant (if applicable) medications
- TTE including assessment of EOA, peak 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 the Echocardiography Core Laboratory procedure guidelines (see study Manual of Operations). It must be provided to the core laboratory for independent analyses.

Note: TTE must be done for all subjects who have a transcatheter valve implanted in the aortic position during the index procedure. Subjects who do not receive a transcatheter valve during the index procedure are not required to have follow-up TTE.

- Complete adverse event (AE, SAE, SADE, UADE, ADE and CEC events) assessment for test device(s) and device deficiencies assessment for test device(s), with associated treatment
- Quality of Life Surveys: Kansas City Cardiomyopathy and SF-12 Quality of Life Questionnaires

  Note: Quality of life will be evaluated by the Kansas City Cardiomyopathy and SF-12 questionnaires at baseline, 1 month, 1 year, and 5 years. A formal health economics analysis may be completed if meaningful clinical results are obtained.
- For subjects enrolled in the CT Imaging Substudy, assessment of prosthetic valve leaflet mobility using 4D CT must be performed per the CT Core Laboratory procedure guidelines (see study Manual of Operations). The 4D CT scans done for the CT Imaging Substudy must be sent to the CT Core Laboratory for independent analyses.

  Note: The CT scans will be read by the CT Core Laboratory and findings will not be provided to local investigators except as noted above. Local reading should be done only for non-cardiac valve findings such as unexpected lung pathology. A study CT scan can be unblinded upon investigator request based on the conditions described in Section **10.10.1** if the event occurs within 2 weeks of the study CT scan.

10.10.3. Annual Follow-up (±45 Days) to 5 Years

All implanted subjects must be evaluated in person at 24, 36, 48, and 60 months (2, 3, 4, and 5 years) after the index procedure, with a window of ±45 days. During the annual follow-up, the following assessments must be completed. The REPRISE IV eCRFs identify the specific data points to be collected.

- NYHA classification
- Modified Rankin Scale score, which must be performed by a neurology professional or certified personnel (external or internal certification); mRS assessors should be independent (not involved with the care of study subjects).
- Current antiplatelet, anticoagulant (if applicable)
- TTE, including assessment of EOA, peak 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 the Echocardiography Core Laboratory procedure guidelines. All TTEs must be forwarded to the core laboratory for independent analyses.

  Note: TTE must be done for all subjects who have a transcatheter valve implanted in the aortic position during the index procedure.

- Complete serious adverse event (SAE, SADE, UADE, and CEC events) assessment for test device(s) and device deficiencies assessment for test device(s) with associated treatment.
- Quality of Life Surveys: Kansas City Cardiomyopathy and SF-12 Quality of Life Questionnaires at 5 years

  Note: Quality of life will be evaluated by the Kansas City Cardiomyopathy and SF-12 questionnaires at baseline, 1 month, 1 year, and 5 years. A formal health economics analysis may be completed if meaningful clinical results are obtained.

10.10.4. Follow-up (±60 Days) at 7 and 10 Years

All implanted subjects must be evaluated in person at 84 and 120 months (7 and 10 years) after the index procedure, with a window of ±60 days. The following assessments must be completed. The REPRISE IV eCRFs identify the specific data points to be collected.

- NYHA classification
- Current antiplatelet, anticoagulant (if applicable)
- TTE, including assessment of effective orifice area, peak and mean aortic valve gradient pressure, aortic regurgitation assessment, peak aortic velocity, and LVEF per the Echocardiography Core Laboratory procedure guidelines. All TTEs must be forwarded to the core laboratory for independent analyses.

  Note: TTE must be done for all subjects who have a transcatheter valve implanted in the aortic position during the index procedure.
- Serious adverse event (SAE, SADE, UADE, and relevant VARC events to be adjudicated by the CEC) assessment for test device(s) and device deficiencies assessment for test device(s) with associated treatment.

  Note: Relevant VARC events to be adjudicated by the CEC include the following: mortality, stroke, spontaneous myocardial infarction, acute kidney injury, repeat procedure for valve-related dysfunction, hospitalization for valve-related symptoms or worsening congestive heart failure (NYHA III or IV), new pacemaker, new onset atrial fibrillation or atrial flutter, prosthetic aortic valve malpositioning (valve migration, valve embolization, or ectopic valve deployment), TAV-in-TAV, prosthetic aortic valve thrombosis and endocarditis.

10.10.5. Follow-up (±60 Days) at 6, 8 and 9 Years

All implanted subjects must be evaluated at 72, 96, and 108 months (6, 8 and 9 years) after the index procedure, with a window of ±60 days. This evaluation may be conducted by telephone. The following assessments must be completed. The REPRISE IV eCRFs identify the specific data points to be collected.

- Current antiplatelet, anticoagulant (if applicable)

- Serious adverse event (SAE, SADE, UADE, and relevant VARC events to be adjudicated by the CEC) assessment for test device(s) and device deficiencies assessment for test device(s) with associated treatment. Please see Section **10.10.4** for a list of relevant VARC events.

10.11. *Study Completion*

All subjects who receive a test device will be evaluated at discharge or 7 days (whichever comes first), 30 days, and then annually up to 10 years post index procedure. Visits in the first 5 years and at 7 and 10 years are office or in-person visits. Evaluations may be conducted by telephone at 6, 8 and 9 years. A subject's participation in the study will be considered complete after the 10-year visit. For subjects who do not receive a test device, participation in the study will be considered complete after the 1-year visit. Any ongoing adverse events after study completion should be managed per standard of care.

10.12. *Source Documents*

When available, original source documents (see **Table 25.2-1** for definition) should be maintained at the investigative center. In lieu of original source documents, certified copies are required to be maintained. A certified copy is a copy (irrespective of the type of media used) of the original record that has been verified (i.e., by a dated signature [PI or as delegated by the PI] or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original. Source documentation includes but is not limited to those items noted in **Table 10.12-1**.

Table 10.12-1: Source Documentation Requirements

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

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

10.13. *Local Laboratory/Vendor Documentation*

Appropriate certifications and documentation records are required to be maintained at the investigative center for local laboratory/vendor work.

11. Statistical Considerations

11.1. *Endpoints*

11.1.1. Primary Endpoint

The primary endpoint is the composite of all-cause mortality and all stroke at 1 year.

11.1.1.1. Statistical Hypothesis for the Primary Endpoint

The statistical hypothesis is that the rate of the primary endpoint (composite of all-cause mortality and all stroke at 1 year) in the Main Cohort is less than the performance goal (PG) of 15.2% (expected rate of 11.1% plus testing margin of 4.1%).

A one-sample z-test will be used to test the one-sided hypothesis that the 1-year primary endpoint rate for LOTUS *Edge* in the Main Cohort is less than the PG:

H_0: $P_{LOTUS\ Edge} \geq PG$

H_1: $P_{LOTUS\ Edge} < PG$

where $P_{LOTUS\ Edge}$ is the primary endpoint rate for the LOTUS *Edge* group and PG is the performance goal.

The primary analysis set for the primary endpoint is the intention-to-treat (ITT) analysis set (see Section **11.2.1**). This endpoint will also be analyzed for the implanted analysis set.

11.1.1.2. Sample Size Parameters for the Primary Endpoint

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

- Expected rate for LOTUS *Edge* = 11.1%*
- Testing margin = 4.1% (37% relative to the expected rate)
- Performance goal (PG) = 15.2% (expected rate of 11.1% plus testing margin of 4.1%)
- Test significance level (α) = 0.025 (1-sided)
- Power = 87.5%
- Number of evaluable subjects = 675
- Expected rate of attrition = 3%
- Total enrollment (evaluable Main Cohort) = 696 subjects

  * Estimated pooled rate from the fixed effect model based on the TAVR arm data from PARTNER II S3i[32] and SURTAVI[34]

11.1.1.3. Success Criteria – Primary Endpoint

If the *P* value from the one-sample z-test is <0.025, it will be concluded that the primary endpoint with the LOTUS *Edge* Valve System is less than the PG. This corresponds to the

one-sided upper 97.5% confidence bound of the observed composite rate of all-cause mortality and all stroke in the Main Cohort at 1 year being < 15.2%.

11.1.1.4. Statistical Methods – Primary Endpoint

All subjects who are enrolled will be eligible for evaluation. Handling of dropouts and missing data will depend on their frequency and the nature of the outcome measure. Sensitivity analyses (e.g., tipping-point analysis) will be performed to assess the impact of subjects with inadequate follow-up (i.e., missing data) on the primary endpoint and to assess the robustness of the conclusion of the primary analysis. Statistical models that account for censored data will be employed in appropriate circumstances (e.g., for time-to-event outcomes). Suspected invalid data will be queried and corrected in the database prior to statistical analysis. Additional information may be found in the statistical analysis plan (SAP).

11.1.2. Baseline Comparability

Baseline data will be summarized separately for subjects in the Main Cohort, Roll-In Cohort, and Bicuspid Nested Registry Cohort. Subject demographics, clinical and neurological history, risk factors, and pre-procedure characteristics will be summarized using descriptive statistics (e.g., mean, standard deviation, n, minimum, maximum) for continuous variables and frequency tables or proportions for discrete variables. Procedural characteristics will be summarized similarly.

11.1.3. Post-procedure Measurements

Post-procedure information will be collected at regularly scheduled follow-up examinations as detailed in the clinical study schedule (see **Table 10.1-1**) and will be summarized using descriptive statistics for continuous variables (e.g., mean, standard deviation, n, minimum, maximum) and frequency tables or proportions for discrete variables. The Kaplan-Meier product-limit method will be used to estimate rates for time-to-event endpoints. Adverse event and SAE rates will be reported. No formal statistical testing will be done for the Roll-In Cohort or Bicuspid Nested Registry Cohort.

11.1.4. Subgroup Analyses

Primary and pre-specified additional endpoints will be summarized and compared for the following subgroups.

- Gender (male and female)

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

For the CT Imaging Substudy, data from the 4D CT scan at 30 days and at 1 year post LOTUS *Edge* valve implantation to assess the prevalence of reduced leaflet mobility will be summarized and the relationship, if any, to clinical events will be explored.

11.2. *General Statistical Methods*

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

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

11.2.1. Analysis Sets

The primary endpoint and additional measurements will be analyzed on an ITT and an implanted basis. For ITT analyses, all subjects who sign the IRB/HREC-approved study ICF (see Section **10.3**) and are enrolled in the trial will be included in the analysis, whether or not a study valve was implanted. For implanted analyses, ITT subjects who had the study valve implanted will be included in the analysis.

For the Main Cohort, the primary endpoint will be analyzed for the ITT and implanted analysis sets. The primary analysis for the primary endpoints will be based on the ITT analysis set.

11.2.2. Control of Systematic Error/Bias

All subjects who have met the inclusion/exclusion criteria, received a positive recommendation from the CRC, and signed the ICF will be eligible for enrollment in the study. The center heart team's assessment of TTE measurements before device placement will contribute to the determination of subject eligibility for the study.

To control for inter-observer variability, data from independent core laboratories (see Section **13.3**) will be used for analysis. These include an echocardiography core laboratory, a CT and procedural angiography core laboratory to assess all CT and procedural angiography data using standard techniques, and an electrocardiography core laboratory to independently analyze protocol-required 12-lead ECGs performed for each subject. Clinical endpoints will also be adjudicated by an independent CEC (Section **21.1.1**).

11.2.3. Reporting Events

For all subjects, all events that occur from the time of enrollment will be reported. For time based clinical events, the cut-off for events for 30-day endpoints will be 30 days, for 1-year endpoints it will be 365 days, and for 2–10-year endpoints it will be 365 days times the number of years. For events at discharge or 7 days post-procedure, the cut-off for events will be the earlier of the date of discharge or 7 days post-procedure for each subject.

11.3. *Data Analyses*

Baseline and outcome variables will be summarized using descriptive statistics for continuous variables (mean, standard deviation, number of observations, minimum and

maximum) and discrete variables (percentage and count/sample). See Section **11.1** for a discussion on analysis of the primary endpoint and additional measurements.

11.3.1. Other Measurements

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

11.3.2. Interim Analyses

No formal interim analyses are planned for the purpose of stopping this trial early for effectiveness or futility. Administrative analyses for regulatory agency review may be performed.

11.3.3. Justification of Pooling

All analyses will be performed using data pooled across clinical centers. An assessment of the poolability of subjects across centers will be made by fitting a logistic regression model with the primary composite endpoint of all death and all stroke and with the center as the main effect. If the *P* value for the coefficient for the center is ≥0.1, the data can be pooled across centers. In the analysis to justify pooling across centers, the centers with fewer than 10 subjects enrolled will be combined into "virtual centers" based on geographic region so that "virtual centers" have ≥10 subjects, but no more than the largest enrolling center.

11.3.4. Multivariable Analyses

Univariate and multivariate analyses will be performed to assess the effect of potential predictors on the primary endpoint as described in the SAP.

11.3.5. Changes to Planned Analyses

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

12. Health Economics Outcomes

A formal health economics analysis may be completed as part of this trial, provided meaningful clinical results are obtained. Quality of life will be evaluated by the Kansas City Cardiomyopathy[118] and SF-12[119] questionnaires at baseline, 1 month, 1 year, and 5 years. These inputs may be used in any health economics analysis performed.

13. Data Management

13.1. *Data Collection, Processing, and Review*

Subject data will be recorded in a limited access secure electronic data capture (EDC) system. Only personnel trained and authorized will have access to the system.

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

The Investigator provides his/her electronic signature on the appropriate eCRFs in compliance with local regulations. A written signature on printouts of the eCRFs must also be provided if required by local regulation. Changes to data previously submitted to 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 center for appropriate response. Center staff will be responsible for resolving all queries in the database.

13.2. *Data Retention*

The Principal Investigator or his/her designee or investigational center will maintain all essential study documents and source documentation that support the data collected on the study subjects in compliance with applicable regulatory requirements. 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 Principal Investigator or his/her designee will take measures to ensure that these essential documents are not accidentally damaged or destroyed. If for any reason the Principal Investigator or his/her designee withdraws responsibility for maintaining these essential documents, custody must be transferred to an individual who will assume responsibility and BSC must receive written notification of this custodial change. Centers are required to inform BSC in writing where paper or electronic files are maintained in case files are stored off site and are not readily available.

13.3. *Core Laboratories*

13.3.1. Echocardiography Core Laboratory

An independent core laboratory will review echocardiography images from all centers and every subject enrolled in this study for qualitative and quantitative analysis. These analyses will minimize bias and inconsistencies by providing an independent interpretation of all measurements using standard techniques. The TTE procedure guideline is provided by the core laboratory in the study Manual of Operations.

13.3.2. CT and Angiography Core Laboratory

An independent core laboratory will centrally assess all of the CT and angiography data in this study to reduce variability. These analyses will minimize bias and inconsistencies by providing an independent interpretation of all measurements using standard techniques. Procedure guidelines are provided by the core laboratory in the study Manual of Operations.

13.3.3. Electrocardiography (ECG) Core Laboratory

All 12-lead ECGs performed at each of the required protocol visits will be sent to an ECG core laboratory (see study Manual of Operations) for independent analyses. These analyses will minimize bias and will provide consistent interpretation of the ECGs.

13.3.4. Histopathology Core Laboratory

If a LOTUS *Edge* valve is explanted during conventional scheduled or emergent surgical valve replacement or during an autopsy, please refer to the study Manual of Operations for recommendations on the explant procedure and shipment of the explanted valve for assessment by an independent histopathology laboratory.

14. Deviations

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

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

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

15. Device Accountability

15.1. *Device Accountability for Products Labelled Investigational*

The investigational devices will be released by the Sponsor or designee to the clinical center only after the center has been initiated and all regulatory approvals as well as required documentation have been collected from the center.

The investigational devices shall be securely maintained and controlled and used only in this clinical study. Additionally, study personnel must follow the instructions related to the storage of the investigational devices as noted in the corresponding IFUs. An electronic interactive response technology (IRT) will be used for investigational device management and accountability during the study.

The Sponsor or designee shall keep records to document the physical location of all investigational devices from shipment of the investigational devices to the investigation centers until return or disposal. The IRT will be used to document reception of the investigational device at a center. Records shall be kept by authorized center study personnel to document the physical location and conditions of storage of all investigational devices. Centers must not dispose of any investigational devices for any reason at the center unless instructed to do so by BSC. Any investigational device that is disposed of at the center must be documented appropriately. Centers must document the reasons for any discrepancy noted in device accountability.

The Principal Investigator or an authorized designee shall keep records documenting the receipt, use, return, transfer, and disposal of the investigational devices, which shall include the following; this will be verified by personnel from BSC or its designee.

- Date of receipt at the center
- Identification of each investigational device (unique identifier or lot number/batch number/serial number, valve size)
- Expiry date, as applicable
- Date of use
- Subject identification
- Date on which the investigational device was returned/explanted from subject, if applicable
- Date of return and quantity of unused, expired, or malfunctioning investigational devices, if applicable.

Written procedures may be required by national regulations.

Once the Investigator and center are notified in writing by BSC that subject enrollment is complete, all unused investigational devices must be returned to BSC or its designee.

15.2. *Commercial Device*

For countries where the introducer sets are commercially available, appropriate information on the size and model will be collected.

16. Compliance

16.1. *Statement of Compliance*

The REPRISE IV study will be conducted in accordance with 21 CFR 814.20 Parts 11, 50, 54 56, and part 812 or 813; the relevant parts of the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practices (GCP) or the International Standard ISO 14155: Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice; ethical principles that have their origins in the Declaration of Helsinki; and applicable individual country/state/local laws and regulations.

The study shall not begin until the required approval/favorable opinion from the IRB/HREC and/or regulatory authority has been obtained, if appropriate. Also, the study shall not begin prior to issuance of the center Authorization to Screen, as provided by the Sponsor. Any additional requirements imposed by the IRB/HREC or regulatory authority shall be followed, if appropriate.

16.2. *Investigator Responsibilities*

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

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

- Prior to beginning the study, sign the Clinical Study Agreement and comply with the Investigator responsibilities as described in such Agreement.
- Prior to beginning the study, sign the Investigator Brochure Signature Page, Investigator Agreement and Protocol Signature page documenting his/her agreement to conduct the study in accordance with the protocol.
- Provide his/her qualifications and experience to assume responsibility for the proper conduct of the study and that of key members of the center team through up-to-date curriculum vitae or other relevant documentation and disclose potential conflicts of

interest, including financial, that may interfere with the conduct of the clinical study or interpretation of results.

- Complete all LOTUS *Edge* Valve System (investigational device) training requirements as detailed in the REPRISE IV Training Plan (Section **16.4.2**).
- Make no changes in or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency; document and explain any deviation from the approved protocol that occurred during the course of the clinical investigation.
- Create and maintain source documents throughout the clinical study and ensure their availability with direct access during monitoring visits or audits; ensure that all clinical-investigation-related records are retained per requirements.
- Ensure the accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor in the CRFs and in all required reports.
- Record, report, and assess (seriousness and relationship to the device/procedure) every adverse event as applicable per the protocol and observed device deficiency.
- Report to BSC, per the protocol requirements, all SAEs and device deficiencies that could have led to a SADE and potential/USADE or UADE.
- Report to the IRB/HREC and regulatory authorities any SAEs and device deficiencies that could have led to a SADE and potential/USADE or UADE, if required by applicable laws or regulations or this protocol or by the IRB/HREC, and supply BSC with any additional requested information related to the safety reporting of a particular event.
- Maintain the device accountability records and control of the investigational device, ensuring that the investigational device is used only by authorized/designated users and in accordance with this protocol and instructions/directions for use.
- Allow the Sponsor and Sponsor representatives to perform monitoring and auditing activities and be accessible to the clinical research monitor or auditor and respond to questions during monitoring visits or audits.
- Allow and support regulatory authorities and the IRB/HREC when performing auditing activities.
- Ensure that informed consent is obtained in accordance with applicable laws, this protocol and local IRB/HREC requirements.
- Provide adequate medical care to a subject during and after a subject's participation in a clinical study in the case of adverse events, as described in the ICF.
- Inform the subject of the nature and possible cause of any adverse events experienced.
- Inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required.

- Provide the subject with well-defined procedures for possible emergency situations related to the clinical study, and make the necessary arrangements for emergency treatment, including decoding procedures for blinded/masked clinical investigations, as needed.
- Ensure that clinical medical records are clearly marked to indicate that the subject is enrolled in this clinical study.
- Ensure that, if appropriate, subjects enrolled in the clinical investigation are provided with some means of showing their participation in the clinical investigation, together with identification and compliance information for concomitant treatment measures (contact address and telephone numbers shall be provided).
- Inform, with the subject's approval or when required by national regulations, the subject's personal physician about the subject's participation in the clinical investigation.
- Make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from clinical investigation while fully respecting the subject's rights.
- Ensure that an adequate investigation center team and facilities exist and are maintained and documented during the clinical investigation.
- Ensure that maintenance and calibration of the equipment relevant for the assessment of the clinical investigation is appropriately performed and documented, where applicable.

16.2.1. Delegation of Responsibility

When specific tasks are delegated by an investigator, including but not limited to conducting the informed consent process, the Principal Investigator is responsible for providing appropriate training, so the delegate is competent to perform the tasks they have been delegated, and adequate supervision of those to whom tasks are delegated. Where there is a sub-investigator at a center, the sub-investigator should not be delegated the primary supervisory responsibility for the center. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

16.3. *Institutional Review Board/Human Research Ethics Committee*

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

A copy of the written IRB/HREC 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 and shipment of investigational product. Prior approval must also be obtained for other materials related to subject recruitment or which will be provided to the subject.

If a protocol revision is necessary which affects the rights, safety or welfare of the subjects or scientific integrity of the data, an amendment is required. Any amendment to the protocol

will require review and approval by the IRB/HREC before the changes are implemented in the study. All changes to the ICF will be IRB/HREC approved; a determination will be made regarding whether a new ICF needs to be obtained from subjects who provided consent using a previously approved ICF. Annual IRB/HREC approval and renewals will be obtained throughout the duration of the study as required by applicable local/country laws or regulations or IRB/HREC requirements. Copies of the Investigator's reports and the IRB/HREC continuance of approval must be provided to the Sponsor.

16.4. *Sponsor Responsibilities*

All information and data sent to BSC and its authorized designee concerning subjects or their participation in this study will be considered confidential by BSC and will be kept confidential in accordance with all applicable laws and regulations. Only authorized BSC personnel, representatives, or designees 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 such as overseeing and improving the performance of its device, new medical research and proposals for developing new medical products or procedures. All data used in the analysis and reporting of this study or shared with a third-party researcher will be without identifiable reference to specific subjects.

Note: Boston Scientific may utilize a contract research organization (CRO) or other contractors to act as its representative for carrying out designated tasks.

Boston Scientific Corporation will keep subjects' health information confidential in accordance with all applicable laws and regulations. Information received during the study will not be used to market to subjects; subject names will not be placed on any mailing lists or sold to anyone for marketing purposes.

16.4.1. Role of Boston Scientific Corporation Representatives

Boston Scientific Corporation personnel (including field clinical engineers and specialists) who are trained in the use of the investigational device will provide technical support to the investigator and other health care personnel (collectively HCP) as needed during LOTUS *Edge* valve implant and testing required by the protocol. Boston Scientific Corporation is also responsible for ensuring investigators are trained on the investigational device(s). Support may include HCP training (see Section **16.4.2** below), addressing HCP questions, or providing clarifications to HCPs concerning the operation of BSC equipment/devices.

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

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

Boston Scientific personnel will not do the following.

- Practice medicine
- Provide medical diagnosis or treatment to subjects
- Discuss a subject's condition or treatment with a subject without the approval and presence of the investigator
- Independently collect critical study data (defined as primary or secondary endpoint data)
- Enter data in electronic data capture systems or on paper case report forms

16.4.2. Training with the Investigational Device

The Sponsor is responsible for providing investigators with the information and training on the LOTUS *Edge* Valve System and iSleeve and Lotus Introducer Sets they need to conduct the study properly. The Sponsor is responsible for maintaining documentation of attendance at each of the training sessions provided.

Training on the LOTUS *Edge* Valve System has been developed that meets the requirements of ISO 5840-3 and includes the following elements.

- Device training to include a detailed description of all device components including a summary of the basic principle of operation and hands-on bench top demonstration using valve and delivery system components in a simulated implantation model.
- Patient selection and device sizing to include a review of the Instructions for Use (IFU) and pre-procedural and procedural imaging techniques to aid in sizing decisions and implantation of the valve.
- Implantation techniques to include a step-by-step review of the procedure (including alternative access, where applicable) while highlighting associated cautions and warnings from the IFU. Training should include video representation of implantation procedural steps and associated fluoroscopic images of each step. Clinical case reviews should be presented to demonstrate intended procedural steps as well as appropriate troubleshooting.
- Proctoring: The investigator and co-investigators as well as the scrub team will be proctored by an individual experienced with the LOTUS *Edge* valve and TAVR on a minimum of 5 implantation procedures. If the proctor or investigators (First Operator and Second Operator) are not satisfied that these initial proctored procedures are sufficient preparation, then subsequent proctoring sessions may be added as needed.

Note 1: If a physician has prior experience implanting the Lotus valve, he/she will be trained per above to the LOTUS *Edge* Valve System prior to re-starting first implants. Further, if the physician was considered proctor-free under the previous Lotus program, a proctor will not be required.

Note 2: For centers that do not have implantation experience with the LOTUS *Edge* Valve System, at least 2 roll-in cases will be performed before enrollment can commence in the Main Cohort or in the Bicuspid Nested Registry. For centers that do not have any previous experience implanting the Lotus valve, the roll-in subjects will be treated under the supervision of a proctor and will count towards the 5 required proctored cases. For centers with prior experience with the Lotus valve who are proctor-free, the roll-in subjects will not require the presence of a proctor.

16.5. *Insurance*

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

17. Monitoring

Monitoring will be performed during the study according to the monitoring plan to assess continued compliance with the protocol and applicable regulations. In addition, the clinical research monitor verifies that study records are adequately maintained, that data are reported in a satisfactory manner with respect to timeliness, adequacy, and accuracy, and that the Principal Investigator continues to have sufficient staff and facilities to conduct the study safely and effectively. The Principal Investigator/institution guarantees direct access to original source documents and/or certified copies (please see Section **10.12**) by BSC personnel, their designees, and appropriate regulatory authorities.

The study may also be subject to a quality assurance audit by BSC or its designees, as well as inspection by appropriate regulatory authorities. It is important that the Principal Investigator and relevant study personnel are available during on-site monitoring visits or audits and that sufficient time is devoted to the process.

18. Potential Risks and Benefits

Risks to clinical subjects associated with their participation in this clinical investigation, arising from the clinical procedures set out in the study protocol, have been identified from prior studies conducted by Boston Scientific Corporation and review of relevant literature, most recently from the Edwards Lifesciences' Placement of Aortic Transcatheter Valves (PARTNER) trial[8,20,22,23], the PARTNER II trial (RCT and SAPIEN 3 intermediate risk arm)[33,41,46], the SAPIEN 3 CE Mark study[75], the CoreValve Extreme Risk study[47], the CoreValve High Risk Study[25], the Evolut R CE Mark study[48], the Surgical Replacement and Transcatheter Aortic Valve Implantation (SURTAVI) trial[34], the EVOLUT R US study[49], the PORTICO Pre-CE Mark study[50], and the PORTICO IDE randomized trial/RESOLVE registry/SAVORY registry[40].

Benefits to subjects anticipated to arise from the use of the investigational device have also been identified. These clinical risks and benefits are summarized below, with an assessment of the balance of risks and benefits to subjects. Potential risks and benefits have been

included in the study-specific template of the ICF provided to the study centers (see Section **20**).

18.1. *Anticipated Adverse Events and Risks Associated with Transcatheter Aortic Valve Replacement*

Adverse events (in alphabetical order) potentially associated with TAVR (including, but not limited to, standard cardiac catheterization, BAV, and the use of anesthesia) as well as additional risks related to the use of the LOTUS *Edge* Valve System and the Lotus and iSleeve Introducer Sets include but may not be limited to the risks listed in **Table 18.1-1** below.

Table 18.1-1: Risks Associated with Transcatheter Aortic Valve Replacement

Abnormal lab values (including anemia and electrolytes)
Abnormal pressure gradient
Allergic reaction (including to medications, anesthesia, contrast, or device materials, including nickel, titanium, tantalum, bovine-derived materials or polyurethanes)
Aneurysm (cardiovascular)
Angina
Arrhythmia or new conduction system injury (including need for pacemaker insertion)
Bleeding or hemorrhage (possibly requiring transfusion or intervention)
Cardiac arrest
Cardiac failure/low cardiac output
Cerebrovascular accident, stroke, transient ischemic attack, or cerebral infarction including asymptomatic neuroimaging findings
Coronary obstruction
Death
Device embolization, misplacement or migration
Emboli (including air, tissue, thrombus or device materials)
Emergency cardiac surgery
Endocarditis
Fever
Heart failure
Hematoma or lymphatic problems or other complications at the access sites
Hemodynamic instability or shock
Hemolysis and/or hemolytic anemia
Hypertension/hypotension
Infection (local and/or systemic, including septicemia)
Inflammation
Mitral valve insufficiency or injury
Myocardial infarction or ischemia
Myocardial or valvular injury (including perforation or rupture)
Nerve injury or neurologic deficits (including encephalopathy)
Non-structural valve dysfunction including implant distortion, improper deployment or sizing

Table 18.1-1: Risks Associated with Transcatheter Aortic Valve Replacement

Pain
Pericardial effusion or cardiac tamponade
Peripheral ischemia or infarction
Permanent disability
Pleural effusion
Pulmonary edema
Renal insufficiency or failure
Respiratory insufficiency or failure
Restenosis (including pannus formation)
Thrombosis/thromboembolism
Valve dysfunction, deterioration or failure
Valve-in-valve (need for additional valve within a valve)
Valve or device thrombosis
Valvular stenosis or regurgitation (central or paravalvular)
Vessel injury (including spasm, trauma, dissection, perforation, rupture, arteriovenous fistula, acute coronary occlusion, or pseudoaneurysm)
Wound healing disorders

Note: Risks are listed in alphabetical order.

As a result of these adverse events, the subject may require medical, percutaneous, or surgical intervention, including re-operation and replacement of the valve. These events may lead to fatal outcomes.

As the LOTUS *Edge* Valve System is an investigational device, uncertainty remains over risks of experiencing some or all of the complications listed above. There may be risks that are unknown at this time.

18.1.1. Hypoattenuated Leaflet Thickening/Reduced Leaflet Motion/Leaflet Thrombosis

Hypoattenuated leaflet thickening (HALT[128]) and reduced leaflet motion (RLM[129]) suggestive of subclinical leaflet thrombosis, as detected by high-resolution CT, has been reported with bioprosthetic TAVR and SAVR valves[40,109,130,131]. It is less common among subjects receiving anticoagulant therapy and, in some cases, has been shown to resolve with such treatment[40,109,110,130-133].

Clinical signs of HALT and RLM include elevation of transvalvular gradients (as determined by echocardiography), central or peripheral thromboembolic events, and unexpected recurrence of heart failure. Computed tomography imaging is recommended to appropriately assess subjects with echocardiographic and/or clinical suspicion of leaflet thrombosis. Additional anticoagulant therapy may be indicated based on symptoms or signs and subject bleeding risk[40,109,110,130-133].

The subset of subjects undergoing 4D CT scans at 30 days and 1 year will be exposed to an additional radiation dose of about 20 millisieverts (mSv), which is equivalent to about 10 years' worth of natural background radiation. The contrast dye used during the image acquisition can cause medical problems such as allergic reactions and increase the risk of worsening kidney function or failure.

18.2. *Risks Associated with the Study Device(s)*

Overall, there are no incremental risks expected with the investigational device(s) compared to similar devices on the market.

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

Risks associated with TAVR and participation in this clinical study are listed above in **Table 18.1-1**.

18.4. *Possible Interactions with Concomitant Medical Treatments*

Medications to be used in REPRISE IV constitute standard of care for TAVR as described in society guidelines[10,121]. Please also see Section **10** for medications to be used in this study.

18.5. *Risk Minimization Actions*

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

Boston Scientific Corporation will employ measures throughout the course of this investigation consistent with the best practices and lessons learned from other ongoing TAVR trials and commercial use to minimize risk for subjects choosing to participate. All efforts will be made to minimize risks by selecting centers that are experienced and skilled in TAVR procedures.

Risk mitigation will be accomplished through the following actions.

- Clearly defining the inclusion/exclusion criteria to ensure only appropriate subjects are enrolled
- Confirmation of eligible subjects by a Case Review Committee, including experienced investigators in TAVR
- Ensuring that treatment and follow-up of the subject are consistent with current medical practices
- Selection of investigators who are experienced and skilled in TAVR procedures
- Completion of training and proctorship provided by the Sponsor

- Performing all procedures in accordance with the IFU, including the preparation of the valve and delivery system
- Dynamic safety review processes, including assessment by the Data Monitoring Committee (DMC, Section **21.1.2**) and CEC (Section **21.1.1**) adjudication of specified events as recommended by VARC[61,62].

In addition to its repositioning and self-centering features designed to facilitate optimal positioning, the LOTUS *Edge* Valve System provides physicians with control throughout the procedure by allowing them to pause, assess, lock, un-lock, incrementally reverse, resheathe and, if needed, retrieve the valve prior to final release. These features help the physician to do the following: place the valve correctly with the first attempt, reposition the device if the initial deployment is considered to be suboptimal, and retrieve the device if during the procedure the decision is made not to implant. The valve's outer seal is also designed to minimize paravalvular leakage.

Anticoagulation medication (e.g., heparin) will be administered during the procedure to reduce the risk of embolism and stroke. Additionally, post-procedure antiplatelet therapy is recommended to minimize any risk of thrombus formation, stroke, or transient ischemic attack. Neurological assessments (NIHSS and mRS) will be performed at each required follow-up visit to identify any change in the neurological status of the subjects as recommended by VARC[61,62].

Cardiac enzyme measurements as well as ECGs post-procedure will be performed to detect periprocedural MI.

Subjects will be carefully monitored during the procedure, hospitalization, and throughout the follow-up period. Serial echocardiograms and electrocardiograms will be used to evaluate valve and general cardiac function. Any abnormal rhythm will be assessed and, if needed, the implantation of a permanent pacemaker will be performed. Annual imaging will also be performed to assess for structural valve frame integrity.

Subjects who are converted to standard surgical aortic valve replacement will be carefully monitored in a method appropriate for their surgical procedure.

Data will be monitored as they are submitted to BSC. Qualified employees of BSC, or a designee under contract, will conduct monitoring visits at the initiation of the study and at interim intervals described in the monitoring plan throughout the course of the study to evaluate protocol compliance and determine if there are any issues that could affect the safety or welfare of any subject in the study.

18.6. *Anticipated Benefits*

18.6.1. Potential Benefits to the TAVR Procedure

Transcatheter aortic valve replacement (TAVR) may offer certain advantages when compared to surgical replacement of the stenotic aortic valve. Known benefits associated

with TAVR, as described in the scientific literature (see summary in Section **4.1.1** of this document and details in the Investigator's Brochure), potentially include the following.

- Minimally invasive procedure and reduced risks related to open heart surgery
- Shorter stay in the intensive care unit and overall hospital stay
- Reduced blood loss
- More rapid recovery
- Reduced need for general anesthesia and associated risks

18.6.2. Potential Benefit Using the LOTUS *Edge* Valve System

Potential benefits that may be associated specifically with use of the LOTUS *Edge* Valve System compared to other TAVR systems include the following.

- Pre-loaded delivery system minimizing time required and potential issues with preparing the device
- Accurate valve placement due to the ability to reposition the valve during deployment
- Device is minimally obstructive to the blood flow and maintains hemodynamic stability through the annulus during delivery because there is no balloon or other obstructive device required for deployment and due to early valve leaflet function
- Reduced need for post-dilation
- Reduced or obviated need for valve-in-valve repeat intervention
- Lower risk of ectopic valve placement and valve migration
- Reduced incidence of paravalvular aortic regurgitation due to the Adaptive Seal

18.7. *Risk to Benefit Rationale*

Review of the aforementioned clinical benefits versus risks takes into account the known risks/benefits that have been identified in the published literature on other TAVR devices. The estimation of risk also includes prior limited clinical experience with the Lotus Valve System including earlier generations of the device design. When used according to the IFU, all known risks associated with the TAVR procedure and the specific use of the LOTUS *Edge* Valve System are mitigated to acceptable limits comparable to existing TAVR devices. The design features of full repositioning and retrievability may improve TAVR procedural safety. The Adaptive Seal may provide long term benefit as it is designed to minimize paravalvular regurgitation, which has been associated with long term mortality in TAVR.

19. Safety Reporting

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

It is the responsibility of the investigator to assess and report to BSC any event that occurs in any of the following categories; reporting requirements are described below in **Table 19.4-1**.

- All serious adverse events
- All device-related adverse events
- All study procedure-related adverse events
- All investigational device deficiencies
- Unanticipated adverse device effects/unanticipated serious adverse device effects
- New findings/updates in relation to already reported events

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

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

Any adverse event required by the protocol, experienced by the study subject after informed consent and once considered enrolled in the study (as defined in Section **9.1**), whether during or subsequent to the procedure, must be recorded in the eCRF.

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

In-patient hospitalization is defined as the subject being admitted to the hospital, with the following exceptions.

- A hospitalization that is uncomplicated and elective/planned (i.e., planned prior to enrollment) does not have to be reported as an SAE.
- If complications or AEs occur during an elective/planned (i.e., planned prior to enrollment) hospitalization after enrollment, the complications and AEs must be reported as AEs or SAEs if they meet the protocol-specified definitions.

Event reporting (eCRF data entry) is required beginning from the time an attempt is made to insert the LOTUS *Edge* Valve System into the subject's femoral artery.

Refer to Section **18** for the known risks associated with the study devices.

Based on the VARC[61,62] recommendations and definitions, the adverse events and/or safety endpoints requiring adjudication by the CEC include the following.

- Mortality: all-cause, 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 events: life-threatening (or disabling) and major (through 5 years)
- Acute kidney injury (≤7 days post index procedure): based on the AKIN System [111,112] Stage 3 (including renal replacement therapy) or Stage 2
- Vascular complications: major (including annular rupture; through 5 years)
- 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
- New onset of atrial fibrillation or atrial flutter
- Coronary obstruction: periprocedural (≤72 hours post index procedure)
- Ventricular septal perforation: periprocedural (≤72 hours post index procedure)
- Mitral apparatus damage: periprocedural (≤72 hours post index procedure)
- Cardiac tamponade: periprocedural (≤72 hours post index procedure)
- Prosthetic aortic valve malpositioning, including valve migration, valve embolization, or ectopic valve deployment
- TAV-in-TAV deployment
- Prosthetic aortic valve thrombosis
- Prosthetic aortic valve endocarditis

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

19.2. *Definitions and Classification*

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

Table 19.2-1: Safety Definitions

Term	Definition
Adverse Event (AE) *Ref: ISO 14155*	Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, whether or not related to the investigational medical device.

Table 19.2-1: Safety Definitions

Term	Definition
Ref: MEDDEV 2.7/3	***Note 1:*** This includes events related to the investigational medical device. ***Note 2:*** This definition includes events related to the procedures involved. ***Note 3:*** For users or other persons, this definition is restricted to events related to the investigational medical device.
Adverse Device Effect (ADE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Adverse event related to the use of an investigational medical device ***Note 1:*** This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device. ***Note 2:*** This definition includes any event resulting from use error or intentional abnormal use of the investigational medical device.
Serious Adverse Event (SAE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	***Note 1:*** This definition meets the reporting objectives and requirements of ISO 14155 and MEDDEV 2.7/3. Adverse event that: a) Led to death, b) Led to serious deterioration in the health of the subject as defined by either: 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, or 3) in-patient hospitalization or prolongation of existing hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function c) Led to fetal distress, fetal death, or a congenital abnormality or birth defect. ***Note 2:*** Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without a serious deterioration in health, is not considered a serious adverse event.
Serious Adverse Device Effect (SADE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated Adverse Device Effect (UADE) *Ref: 21 CFR Part 812*	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.
Unanticipated Serious Adverse Device Effect (USADE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report. ***Note****:* Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

Table 19.2-1: Safety Definitions

Term	Definition
Device Deficiency *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	An inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer.

19.3. *Relationship to Study Device(s)*

The Investigator must assess the relationship of the reportable AE/SAE to the study device and procedure. See criteria in **Table 19.3-1**:

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

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

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

Classification	Description
Probably Related *Ref: MEDDEV 2.7/3*	The relationship with the use of the investigational device seems relevant and/or the event cannot be reasonably explained by another cause, but additional information may be obtained.
Causal Relationship *Ref: MEDDEV 2.7/3*	The serious event is associated with the investigational device or with procedures beyond reasonable doubt when: • the event is a known side effect of the product category the device belongs to or of similar devices and procedures; • the event has a temporal relationship with investigational device use/application or procedures; • the event involves a body-site or organ that: - the investigational device or procedures are applied to; - the investigational device or procedures have an effect on; • the serious event follows a known response pattern to the medical device (if the response pattern is previously known); • the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible); • other possible causes (e.g. an underlying or concurrent illness/clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; • harm to the subject is due to error in use; • the event depends on a false result given by the investigational device used for diagnosis, when applicable; • In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

19.4. *Investigator Reporting Requirements*

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

Note: 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.

Table 19.4-1: Investigator Reporting Requirements

Event Classification	**Communication Method**	**Communication Timeline (premarket studies)** (MEDDEV 2.7/3: CLINICAL INVESTIGATIONS: SERIOUS ADVERSE EVENT REPORTING UNDER DIRECTIVES 90/385/EEC AND 93/42/EEC)
Unanticipated Adverse Device Effect / Unanticipated Serious Adverse Device Effect (UADE/USADE)	Complete AE eCRF page with all available new and updated information.	• Within 1 business day of first becoming aware of the event. • Terminating at the end of the study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• At request of Sponsor.
Serious Adverse Event (SAE)	Complete AE eCRF page with all available new and updated information.	• Within 3 calendar days of first becoming aware of the event or as per local/regional regulations. • Reporting required through the end of the study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• At request of Sponsor
Serious Adverse Device Effects (SADE)	Complete AE eCRF page with all available new and updated information.	• Within 3 calendar days of first becoming aware of the event or as per local/regional regulations. • Reporting required through the end of the study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• When documentation is available • At Sponsor request.
Device Deficiencies (including but not limited to failures, malfunctions, and product nonconformities) ***Note:*** Any Investigational Device Deficiency that might	Complete eCRF page with all available new and updated information.	• Within 3 calendar days of first becoming aware of the event. • Reporting required through 12 months

Table 19.4-1: Investigator Reporting Requirements

Event Classification	Communication Method	Communication Timeline (premarket studies) (MEDDEV 2.7/3: CLINICAL INVESTIGATIONS: SERIOUS ADVERSE EVENT REPORTING UNDER DIRECTIVES 90/385/EEC AND 93/42/EEC)
have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable event.	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• At request of Sponsor
Adverse Event including Adverse Device Effects (AE/ADE)	Complete AE eCRF page, which contains such information as date of AE, treatment of AE resolution, assessment of seriousness and relationship to the device.	• In a timely manner (e.g., recommend within 10 business days) after becoming aware of the information • Reporting required through 12 months
	Provide all relevant source documentation (de-identified/pseudonymized) for reported event.	• At request of Sponsor

Note: The AE eCRF page contains information such as date of AE, treatment of AE resolution, assessment of seriousness, and relationship to the device.

Please note that pre-market studies are clinical studies with investigational devices or with medical devices that bear the regulatory approval and are not being used for the same approved indications.

Abbreviations: AE=adverse event; eCRF=electronic case report form

19.5. *Device Deficiencies*

Complaint reporting of any device deficiencies for any commercially available products used should be carried out using the manufacturer's processes.

19.5.1. Boston Scientific Device Deficiencies

All device deficiencies (including but not limited to failures, malfunctions, use errors, product nonconformities, and inadequacy in the information supplied by the manufacturer) related to the investigational device or future iterations must be documented on the appropriate eCRF and reported to BSC. If possible, the device should be returned to BSC for analysis. Instructions for returning the investigational device will be provided in the study Manual of Operations. If it is not possible to return the device, the investigator should document why the device was not returned and the final disposition of the device. Device

deficiencies, failures, and malfunctions should also be documented in the subject's medical record.

Device deficiencies and other device issues should not be reported as AEs. Instead, they should be reported on the appropriate eCRF. If an AE results from a device deficiency or other device issue, the AE must be reported on the appropriate eCRF.

Device deficiencies that did not lead to an AE but could have led to a SAE if a) suitable action had not been taken, or b) intervention had not been made, or c) circumstances had been less fortunate must be reported as described in **Table 19.4-1**.

19.6. *Reporting to Regulatory Authorities / IRBs / HRECs / Investigators*

Boston Scientific Corporation will notify all participating study centers if UADEs, SAEs, SADEs, or investigational device deficiencies occur which imply a possible increase in the anticipated risk of the procedure or use of the device or if the occurrence of certain SAEs/SADEs requires changes to the protocol or the conduct of the study in order to further minimize the unanticipated risks.

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

The Principal Investigator is responsible for informing the IRB/HREC and regulatory authorities of UADEs, SADEs, SAEs, Device Deficiencies and/or other CEC events as applicable according to local reporting requirements.

20. Informed Consent

Subject participation in this clinical study is voluntary. Informed Consent is required from each subject or his/her legally authorized representative. The Investigator is responsible for ensuring that Informed Consent is obtained prior to the use of any investigational devices, study-required procedures and/or testing, or data collection.

The obtaining and documentation of Informed Consent must be in accordance with the principles of the Declaration of Helsinki, the relevant parts of ISO 14155 and the ICH guidelines for GCP, any applicable national regulations, and local Ethics Committee and/or Regulatory authority body, as applicable. The ICF must be accepted by BSC or its delegate (e.g. CRO), and approved by the center's IRB/HREC, or central IRB/HREC, if applicable.

Boston Scientific Corporation will provide a study-specific template of the ICF to investigators participating in this study. The ICF template may be modified to meet the requirements of the investigative center's IRB/HREC. Any modification requires acceptance from BSC or authorized representative 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/HREC approval prior to their use. Privacy language shall be included in the body of the form or as a separate form as applicable.

The process of obtaining Informed Consent shall at a minimum include the following steps, as well as any other steps required by applicable laws, rules, regulations and guidelines:

- be conducted by the Principal Investigator or designee authorized to conduct the process,
- include a description of all aspects of the clinical study that are relevant to the subject's decision to participate throughout the clinical study,
- avoid any coercion of or undue influence of subjects to participate,
- not waive or appear to waive subject's legal rights,
- use native language that is non-technical and understandable to the subject or his/her legal representative,
- provide ample time for the subject to consider participation and ask questions if necessary,
- ensure important new information is provided to new and existing subjects throughout the clinical study.

The ICF shall always be signed and personally dated by the subject or legal representative competent to sign the ICF under the applicable laws, rules, regulations and guidelines and by the investigator or an authorized designee responsible for conducting the informed consent process. If a legal representative signs the ICF, the subject shall be asked to provide informed consent for continued participation as soon as his/her medical condition allows. The original signed ICF will be retained by the center and a copy of the signed and dated document and any other written information must be given to the person signing the form.

Failure to obtain subject consent will be reported by BSC to the applicable regulatory body according to their requirements (e.g., the United States Food and Drug Administration [FDA] requirement is within 5 working days of learning of such an event). Any violations of the informed consent process must be reported as deviations to the Sponsor and local regulatory authorities (e.g. IRB/HREC), as appropriate.

If new information becomes available that can significantly affect a subject's future health and medical care, that information shall be provided to the affected subject(s) in written form via a revised ICF or, in some situations, enrolled subjects may be requested to sign and date an addendum to the ICF. In addition to new significant information during the course of a study, other situations may necessitate revision of the ICF, such as if there are amendments to the applicable laws, protocol, a change in Principal Investigator, administrative changes, or following annual review by the IRB/HREC. The new version of the ICF must be approved by the IRB/HREC. Boston Scientific Corporation approval is required if changes to the revised ICF are requested by the center's IRB/HREC. The IRB/HREC will determine the subject population to be re-consented.

Study personnel should explain that even if a subject agrees to participate in the study and signs an ICF, the heart team and/or the CRC may determine that the subject is not a suitable candidate for the study and/or TAVR procedure. A confidential Screening/Enrollment Log

will be maintained by the center to document select information about candidates who fail to meet the general or "other specific" entry criteria.

21. Committees

21.1. *Safety Monitoring Process*

To promote early detection of safety issues, the Clinical Events Committee (CEC) and Data Monitoring Committee (DMC; see below) will provide evaluations of safety events. Success of this program requires dynamic collection of unmonitored data as soon as the event is reported. This is expedited through the Sponsor or designee, which is responsible for coordinating the collection of information for the subject dossier from the centers and core laboratories. During regularly scheduled monitoring activities, clinical research monitors will support the dynamic reporting process through their review of source document and other data information. The BSC Medical Safety group includes physicians with expertise in cardiology and with the necessary therapeutic and subject matter expertise to evaluate and classify the events into the categories outlined above (Section **19**).

21.1.1. Clinical Events Committee

A Clinical Events Committee (CEC) will be used in this study. A CEC is an independent group of individuals with pertinent expertise, including cardiovascular interventional therapy, cardiovascular surgery, and neurology, which reviews and adjudicates important endpoints and relevant adverse events reported by study investigators. The CEC will review a safety event dossier, which may include copies of subject source documents provided by study centers and adjudicate study endpoint related clinical events. The responsibilities, qualifications, membership, and committee procedures of the CEC are outlined in the CEC Charter.

21.1.2. Data Monitoring Committee

The Data Monitoring Committee (DMC) is responsible for the oversight review of all AEs. The DMC will include leading experts in cardiovascular interventional therapy, cardiovascular surgery, and biostatistics who are not participating in the study and who have no affiliation with BSC. During the course of the study, the DMC will review accumulating safety data to monitor the incidence of CEC events and other trends that would warrant modification or termination of the study. Responsibilities, qualifications, membership, and committee procedures are outlined in the DMC Charter.

21.2. *Case Review Committee*

A Case Review Committee (CRC) will be comprised of experienced cardiac surgeons and interventional cardiologists, including the Study Coordinating PIs, Center PIs, other Investigators, Proctors and Medical Consultants experienced in TAVR for their clinical/medical expertise, and the Sponsor for technical expertise on the LOTUS *Edge* Valve

System requirements. This committee will be responsible for the review of subject screening data to confirm eligibility given the increased surgical risk of the subject population being studied and to ensure consistency of subjects enrolled across study centers. Responsibilities, qualifications, membership, and committee procedures are outlined in the CRC Charter. Minutes are written for each CRC review session and the decisions are documented in these minutes and provided to the centers as appropriate.

21.3. *Steering Committee*

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

22. Suspension or Termination

22.1. *Premature Termination of the Study*

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

22.1.1. Criteria for Premature Termination of the Study

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

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

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

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

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

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

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

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

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

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

Boston Scientific Corporation reserves the right to stop the inclusion of subjects at a study center at any time after the study initiation visit if no subjects have been enrolled for a period beyond 4 months after center initiation, or if the center has multiple or severe protocol violations/noncompliance without justification and/or fails to follow remedial actions.

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

23. Publication Policy

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

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

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

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

24. Bibliography

1. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. Lancet 2006;368:1005-11.
2. Joseph J, Naqvi SY, Giri J, Goldberg S. Aortic stenosis: pathophysiology, diagnosis, and therapy. Am J Med 2017;130:253-63.
3. Kanwar A, Thaden JJ, Nkomo VT. Management of patients with aortic valve stenosis. Mayo Clin Proc 2018;93:488-508.
4. Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2017;135:e1159–e95.
5. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J 2017;38:2739-91.
6. Iung B, Cachier A, Baron G, et al. Decision-making in elderly patients with severe aortic stenosis: why are so many denied surgery? Eur Heart J 2005;26:2714-20.
7. Varadarajan P, Kapoor N, Bansal RC, Pai RG. Clinical profile and natural history of 453 nonsurgically managed patients with severe aortic stenosis. Ann Thorac Surg 2006;82:2111-5.
8. Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med 2010;363:1597-607.
9. Hara H, Pedersen WR, Ladich E, et al. Percutaneous balloon aortic valvuloplasty revisited: time for a renaissance? Circulation 2007;115:e334-8.
10. Holmes DR, Jr., Mack MJ, Kaul S, et al. 2012 ACCF/AATS/SCAI/STS Expert consensus document on transcatheter aortic valve replacement. J Am Coll Cardiol 2012;59:1200-54.
11. Delgado V, Ewe SH, Ng AC, et al. Multimodality imaging in transcatheter aortic valve implantation: key steps to assess procedural feasibility. EuroIntervention 2010;6:643-52.

12. Smith LA, Dworakowski R, Bhan A, et al. Real-time three-dimensional transesophageal echocardiography adds value to transcatheter aortic valve implantation. J Am Soc Echocardiogr 2013;26:359-69.
13. Leipsic J, Yang TH, Min JK. Computed tomographic imaging of transcatheter aortic valve replacement for prediction and prevention of procedural complications. Circ Cardiovasc Imaging 2013;6:597-605.
14. Kasel AM, Cassese S, Bleiziffer S, et al. Standardized imaging for aortic annular sizing: implications for transcatheter valve selection. J Am Coll Cardiol Img 2013;6:249-62.
15. Piazza N, Wenaweser P, van Gameren M, et al. Relationship between the logistic EuroSCORE and the Society of Thoracic Surgeons Predicted Risk of Mortality score in patients implanted with the CoreValve ReValving system--a Bern-Rotterdam Study. Am Heart J 2010;159:323-9.
16. De Feo M, Vicchio M, Della Corte A, et al. Lack of definite indication criteria for choosing between transcatheter implantation and surgical replacement of the aortic valve. J Cardiovasc Med (Hagerstown) 2013;14:158-63.
17. D'Ascenzo F, Ballocca F, Moretti C, et al. Inaccuracy of available surgical risk scores to predict outcomes after transcatheter aortic valve replacement. J Cardiovasc Med (Hagerstown) 2013;14:894-8.
18. Lichtenstein KM, Kim JM, Gao M, et al. Surgical risk algorithm as a measure of successful adoption of transapical transcatheter aortic valve implantation. J Thorac Cardiovasc Surg 2014;146:1524-8.
19. Stortecky S, Schoenenberger AW, Moser A, et al. Evaluation of multidimensional geriatric assessment as a predictor of mortality and cardiovascular events after transcatheter aortic valve implantation. J Am Coll Cardiol Intv 2012;5:489-96.
20. Makkar RR, Fontana GP, Jilaihawi H, et al. Transcatheter aortic-valve replacement for inoperable severe aortic stenosis. N Engl J Med 2012;366:1696-704.
21. Kapadia SR, Tuzcu EM, Makkar RR, et al. Long-term outcomes of inoperable patients with aortic stenosis randomized to transcatheter aortic valve replacement or standard therapy. Circulation 2014;130:1483-92.
22. Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med 2011;364:2187-98.
23. Kodali SK, Williams MR, Smith CR, et al. Two-year outcomes after transcatheter or surgical aortic-valve replacement. N Engl J Med 2012;366:1686-95.
24. Mack MJ, Leon MB, Smith CR, et al. 5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. Lancet 2015;385:2477-84.
25. Adams DH, Popma JJ, Reardon MJ, et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis. N Engl J Med 2014;370:1790-8.

26. Reardon MJ, Adams DH, Kleiman NS, et al. 2-Year outcomes in patients undergoing surgical or self-expanding transcatheter aortic valve replacement. J Am Coll Cardiol 2015;66:113-21.

27. Deeb GM, Reardon MJ, Chetcuti S, et al. 3-Year outcomes in high-risk patients who underwent surgical or transcatheter aortic valve replacement. J Am Coll Cardiol 2016;67:2565-74.

28. Durko AP, Osnabrugge RL, Kappetein AP. Long-term outlook for transcatheter aortic valve replacement. Trends Cardiovasc Med 2018;28:174-83.

29. Rogers T, Thourani VH, Waksman R. Transcatheter aortic valve replacement in intermediate- and low-risk patients. J Am Heart Assoc 2018;7:e007147.

30. Piazza N, Kalesan B, van Mieghem N, et al. A 3-center comparison of 1-year mortality outcomes between transcatheter aortic valve implantation and surgical aortic valve replacement on the basis of propensity score matching among intermediate-risk surgical patients. J Am Coll Cardiol Intv 2013;6:443-51.

31. D'Errigo P, Barbanti M, Ranucci M, et al. Transcatheter aortic valve implantation versus surgical aortic valve replacement for severe aortic stenosis: Results from an intermediate risk propensity-matched population of the Italian OBSERVANT study. Int J Cardiol 2013;167:1945-52.

32. Thourani VH, Kodali S, Makkar RR, et al. Transcatheter aortic valve replacement versus surgical valve replacement in intermediate-risk patients: a propensity score analysis. Lancet 2016;387:2218-25.

33. Leon MB, Smith CR, Mack MJ, et al. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. N Engl J Med 2016;374:1609-20.

34. Reardon MJ, Van Mieghem NM, Popma JJ, et al. Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. N Engl J Med 2017;376:1321-31.

35. Siontis GC, Praz F, Pilgrim T, et al. Transcatheter aortic valve implantation vs. surgical aortic valve replacement for treatment of severe aortic stenosis: a meta-analysis of randomized trials. Eur Heart J 2016;37:3503-12.

36. Villablanca PA, Mathew V, Thourani VH, et al. A meta-analysis and meta-regression of long-term outcomes of transcatheter versus surgical aortic valve replacement for severe aortic stenosis. Int J Cardiol 2016;225:234-43.

37. Otto CM, Kumbhani DJ, Alexander KP, et al. 2017 ACC expert consensus decision pathway for transcatheter aortic valve replacement in the management of adults with aortic stenosis. J Am Coll Cardiol 2017;69:1313-46.

38. Bonow RO, Brown AS, Gillam LD, et al. ACC/AATS/AHA/ASE/EACTS/HVS/SCA/SCAI/SCCT/SCMR/STS 2017 Appropriate use criteria for the treatment of patients with severe aortic stenosis: a report of the American College of Cardiology Appropriate Use Criteria Task Force, American Association for Thoracic Surgery, American Heart Association, American Society of

Echocardiography, European Association for Cardio-Thoracic Surgery, Heart Valve Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and Society of Thoracic Surgeons. J Am Coll Cardiol 2017;70:2566-98.

39. Laschinger JC, Wu C, Ibrahim NG, Shuren JE. Reduced leaflet motion in bioprosthetic aortic valves — the FDA perspective. N Engl J Med 2015;373:1996-8.
40. Makkar RR, Fontana G, Jilaihawi H, et al. Possible subclinical leaflet thrombosis in bioprosthetic aortic valves. N Engl J Med 2015;373:2015-24.
41. Webb JG, Doshi D, Mack MJ, et al. A randomized evaluation of the SAPIEN XT Transcatheter Heart Valve System in patients with aortic stenosis who are not candidates for surgery. J Am Coll Cardiol Intv 2015;8:1797-806.
42. Thyregod HGH, Steinbrüchel DA, Ihlemann N, et al. Transcatheter versus surgical aortic valve replacement in patients with severe aortic valve stenosis: 1-year results from the all-comers NOTION randomized clinical trial. J Am Coll Cardiol 2015;65:2184-94.
43. Abdel-Wahab M, Mehilli J, Frerker C, et al. Comparison of balloon-expandable vs self-expandable valves in patients undergoing transcatheter aortic valve replacement: The CHOICE randomized clinical trial. JAMA 2014;311:1503-14.
44. Feldman TE, Reardon MJ, Rajagopal V, et al. Effect of mechanically expanded vs self-expanding transcatheter aortic valve replacement on mortality and major adverse clinical events in high-risk patients with aortic stenosis: the REPRISE III randomized clinical trial. JAMA 2018;319:27-37.
45. Fearon WF, Kodali S, Doshi D, et al. Outcomes after transfemoral transcatheter aortic valve replacement: a comparison of the randomized PARTNER (Placement of AoRTic TraNscathetER Valves) trial with the NRCA (Nonrandomized Continued Access) registry. J Am Coll Cardiol Intv 2014;7:1245-51.
46. Kodali S, Thourani VH, White J, et al. Early clinical and echocardiographic outcomes after SAPIEN 3 transcatheter aortic valve replacement in inoperable, high-risk and intermediate-risk patients with aortic stenosis. Eur Heart J 2016;37:2252-62.
47. Popma JJ, Adams DH, Reardon MJ, et al. Transcatheter aortic valve replacement using a self-expanding bioprosthesis in patients with severe aortic stenosis at extreme risk for surgery. J Am Coll Cardiol 2014;63:1972-81.
48. Manoharan G, Walton AS, Brecker SJ, et al. Treatment of symptomatic severe aortic stenosis with a novel resheathable supra-annular self-expanding transcatheter aortic valve system. J Am Coll Cardiol Intv 2015;8:1359-67.
49. Popma JJ, Reardon MJ, Khabbaz K, et al. Early clinical outcomes after transcatheter aortic valve replacement using a novel self-expanding bioprosthesis in patients with

severe aortic stenosis who are suboptimal for surgery: Results of the Evolut R U.S. Study. J Am Coll Cardiol Intv 2017;10:268-75.

50. Linke A, Holzhey D, Möllmann H, et al. Treatment of aortic stenosis with a self-expanding, resheathable transcatheter valve: one-year results of the international multicenter Portico Transcatheter Aortic Valve Implantation System study. Circ Cardiovasc Interv 2018;11:e005206.

51. Abdel-Wahab M, Neumann FJ, Mehilli J, et al. 1-Year outcomes after transcatheter aortic valve replacement with balloon-expandable versus self-expandable valves: results from the CHOICE randomized clinical trial. J Am Coll Cardiol 2015;66:791-800.

52. Bax JJ, Delgado V, Bapat V, et al. Open issues in transcatheter aortic valve implantation. Part 2: procedural issues and outcomes after transcatheter aortic valve implantation. Eur Heart J 2014;35:2639-54.

53. Geisbüsch S, Bleiziffer S, Mazzitelli D, Ruge H, Bauernschmitt R, Lange R. Incidence and management of CoreValve dislocation during transcatheter aortic valve implantation. Circ Cardiovasc Interv 2010;3:531-6.

54. Lerakis S, Hayek SS, Douglas PS. Paravalvular aortic leak after transcatheter aortic valve replacement: current knowledge. Circulation 2013;127:397-407.

55. Van Belle E, Juthier F, Susen S, et al. Postprocedural aortic regurgitation in balloon-expandable and self-expandable transcatheter aortic valve replacement procedures: analysis of predictors and impact on long-term mortality: insights from the FRANCE2 Registry. Circulation 2014;129:1415-27.

56. Kodali S, Pibarot P, Douglas PS, et al. Paravalvular regurgitation after transcatheter aortic valve replacement with the Edwards Sapien Valve in the PARTNER trial: characterizing patients and impact on outcomes. Eur Heart J 2015;36:449-56.

57. Athappan G, Patvardhan E, Tuzcu EM, et al. Incidence, predictors and outcomes of aortic regurgitation after transcatheter aortic valve replacement: Meta-analysis and systematic review of literature. J Am Coll Cardiol 2013;61:1585-95.

58. Hayashida K, Lefèvre T, Chevalier B, et al. Impact of post-procedural aortic regurgitation on mortality after transcatheter aortic valve implantation. J Am Coll Cardiol Intv 2012;5:1247-56.

59. Ando T, Briasoulis A, Telila T, Afonso L, Grines CL, Takagi H. Does mild paravalvular regurgitation post transcatheter aortic valve implantation affect survival? A meta-analysis. Catheter Cardiovasc Interv 2018;91:135-47.

60. Meredith IT, Hood KL, Haratani N, Allocco DJ, Dawkins KD. The Lotus™ Valve: a next-generation transcatheter aortic valve replacement system. EuroIntervention 2012;8:Q70-Q4.

61. Leon MB, Piazza N, Nikolsky E, et al. Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials: a consensus report from the Valve Academic Research Consortium. J Am Coll Cardiol 2011;57:253-69.

62. Kappetein AP, Head SJ, Genereux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. J Am Coll Cardiol 2012;60:1438-54.

63. Meredith IT, Worthley SG, Whitbourn RJ, et al. Transfemoral aortic valve replacement with the repositionable Lotus Valve System in high surgical risk patients: The REPRISE I study. EuroIntervention 2014;9:1264-70.

64. Gooley R, Worthley SG, Whitbourn RJ, et al. Final results from the REPRISE I study: five-year clinical outcomes with the repositionable and fully retrievable Lotus Valve System. EuroIntervention 2018; 14:e1180-e2.

65. Kim K, DeMets DL. Design and analysis of group sequential tests based on the type I error spending rate function. Biometrika 1987;74:149-54.

66. Meredith IT, Walters D, Dumonteil N, et al. Transcatheter aortic valve replacement for severe symptomatic aortic stenosis using a repositionable valve system: 30-day primary endpoint results from the REPRISE II study. J Am Coll Cardiol 2014;64:1339-48.

67. Meredith IT. Two-year outcomes with the fully repositionable and retrievable Lotus™ transcatheter aortic replacement valve in 120 high-risk surgical patients with severe aortic stenosis: results from the REPRISE II CE-Mark study. TCT. San Francisco 2015.

68. Meredith IT, Walters D, Dumonteil N, et al. One-year outcomes with the fully repositionable and retrievable Lotus™ transcatheter aortic replacement valve in 120 high-risk surgical patients with severe aortic stenosis: results from the REPRISE II study. J Am Coll Cardiol Intv 2016;9:376-84.

69. Meredith IT. Three-year outcomes with the fully repositionable and retrievable Lotus™ transcatheter aortic replacement valve in 120 high-risk surgical patients with severe aortic stenosis: results from the REPRISE II CE-Mark study. TCT. Washington, D.C. 2016.

70. Hildick-Smith D, Walters DL, Dumonteil N, et al. Four-year outcomes with the fully repositionable and retrievable Lotus transcatheter aortic valve: results from the REPRISE II study. TCT. Denver, CO 2017.

71. Dumonteil N, Walters D, Worthley SG, et al. Final 5-year outcomes of the REPRISE II study: long-term outcomes with the fully repositionable and retrievable Lotus transcatheter aortic valve. TCT. San Diego, CA 2018.

72. Meredith IT, Dumonteil N, Blackman DJ, et al. Repositionable percutaneous aortic valve replacement: 30-day outcomes in 250 high surgical risk patients in the REPRISE II extended trial cohort. EuroPCR London Valves. London 2014.

73. Webb JG, Wood DA. Current status of transcatheter aortic valve replacement. J Am Coll Cardiol 2012;60:483-92.

74. Möllmann H, Kim WK, Kempfert J, Walther T, Hamm C. Complications of transcatheter aortic valve implantation (TAVI): how to avoid and treat them. Heart 2015;101:900-8.

75. Webb J, Gerosa G, Lefèvre T, et al. Multicenter evaluation of a next-generation balloon-expandable transcatheter aortic valve. J Am Coll Cardiol 2014;64:2235-43.

76. Tarantini G, Mojoli M, Purita P, et al. Unravelling the (arte)fact of increased pacemaker rate with the Edwards SAPIEN 3 valve. EuroIntervention 2015;11:343-50.

77. Buellesfeld L, Stortecky S, Heg D, et al. Impact of permanent pacemaker implantation on clinical outcome among patients undergoing transcatheter aortic valve implantation. J Am Coll Cardiol 2012;60:493-501.

78. Biner S, Michowitz Y, Leshem-Rubinow E, et al. Hemodynamic impact and outcome of permanent pacemaker implantation following transcatheter aortic valve implantation. Am J Cardiol 2014;113:132-7.

79. Regueiro A, Abdul-Jawad Altisent O, Del Trigo M, et al. Impact of new-onset left bundle branch block and periprocedural permanent pacemaker implantation on clinical outcomes in patients undergoing transcatheter aortic valve replacement: a systematic review and meta-analysis. Circ Cardiovasc Interv 2016;9:e003635.

80. Dizon JM, Nazif TM, Hess PL, et al. Chronic pacing and adverse outcomes after transcatheter aortic valve implantation. Heart 2015;101:1665-71.

81. Nazif TM, Dizon JM, Hahn RT, et al. Predictors and clinical outcomes of permanent pacemaker implantation after transcatheter aortic valve replacement: the PARTNER (Placement of AoRtic TraNscathetER Valves) Trial and Registry. J Am Coll Cardiol Intv 2015;8:60-9.

82. Urena M, Webb JG, Tamburino C, et al. Permanent pacemaker implantation after transcatheter aortic valve implantation: impact on late clinical outcomes and left ventricular function. Circulation 2014;129:1233-43.

83. Abdel-Wahab M, Zahn R, Horack M, et al. Aortic regurgitation after transcatheter aortic valve implantation: incidence and early outcome. Results from the German Transcatheter Aortic Valve Interventions registry. Heart 2011;97:899-906.

84. Tamburino C, Capodanno D, Ramondo A, et al. Incidence and predictors of early and late mortality after transcatheter aortic valve implantation in 663 patients with severe aortic stenosis. Circulation 2011;123:299-308.

85. Gotzmann M, Korten M, Bojara W, et al. Long-term outcome of patients with moderate and severe prosthetic aortic valve regurgitation after transcatheter aortic valve implantation. Am J Cardiol 2012;110:1500-6.

86. Mohr FW, Holzhey D, Möllmann H, et al. The German Aortic Valve Registry: 1-year results from 13,680 patients with aortic valve disease. Eur J Cardiothorac Surg 2014;46:808-16.

87. Abdel-Wahab M, Comberg T, Buttner HJ, et al. Aortic regurgitation after transcatheter aortic valve implantation with balloon- and self-expandable prostheses: a pooled analysis from a 2-center experience. J Am Coll Cardiol Intv 2014;7:284-92.

88. Dworakowski R, Wendler O, Halliday B, et al. Device-dependent association between paravalvar aortic regurgitation and outcome after TAVI. Heart 2014;100:1939-45.

89. Jerez-Valero M, Urena M, Webb JG, et al. Clinical impact of aortic regurgitation after transcatheter aortic valve replacement: insights into the degree and acuteness of presentation. J Am Coll Cardiol Intv 2014;7:1022-32.

90. Ewe SH, Muratori M, Van Der Kley F, et al. Effect of aortic regurgitation following transcatheter aortic valve implantation on outcomes. Am J Cardiol 2015;115:664-9.

91. O'Sullivan KE, Gough A, Segurado R, Barry M, Sugrue D, Hurley J. Is valve choice a significant determinant of paravalular leak post-transcatheter aortic valve implantation? A systematic review and meta-analysis. Eur J Cardiothorac Surg 2014;45:826-33.

92. Meredith IT, Dumonteil N, Blackman DJ, et al. Two-year outcomes with a fully repositionable and retrievable percutaneous aortic valve in 250 high surgical risk patients: Results from the REPRISE II trial extended cohort. EuroPCR London Valves. London 2016.

93. Meredith IT, Dumonteil N, Blackman DJ, et al. Repositionable percutaneous aortic valve implantation with the Lotus valve: 30-day and 1-year outcomes in 250 high-risk surgical patients. EuroIntervention 2017;13:788-95.

94. Tchétché D, Dumonteil N, Blackman DJ, et al. Three-year outcomes with a fully repositionable and retrievable percutaneous aortic valve in 250 high surgical risk patients: results from the REPRISE II trial extended cohort. EuroPCR London Valves. London 2017.

95. Blackman DJ, Dumonteil N, Tchétché D, et al. Four-year outcomes with a fully repositionable and retrievable percutaneous aortic valve in 250 high surgical risk patients: Results from the REPRISE II trial extended cohort. EuroPCR London Valves. London 2018.

96. Falk V, Wohrle J, Hildick-Smith D, et al. Safety and efficacy of a repositionable and fully retrievable aortic valve used in routine clinical practice: the RESPOND Study. Eur Heart J 2017;38:3359-66

97. Van Mieghem NM, Wöhrle J, Hildick-Smith D, et al. The RESPOND study at one-year: primary endpoint outcomes with a repositionable and fully retrievable aortic valve in routine clinical practice. EuroPCR. Paris 2017.

98. Philip F, Faza NN, Schoenhagen P, et al. Aortic annulus and root characteristics in severe aortic stenosis due to bicuspid aortic valve and tricuspid aortic valves:

implications for transcatheter aortic valve therapies. Catheter Cardiovasc Interv 2015;86:E88-98.

99. Watanabe Y, Chevalier B, Hayashida K, et al. Comparison of multislice computed tomography findings between bicuspid and tricuspid aortic valves before and after transcatheter aortic valve implantation. Catheter Cardiovasc Interv 2015;86:323-30.
100. Guyton RA, Padala M. Transcatheter aortic valve replacement in bicuspid aortic stenosis: early success but concerning red flags. J Am Coll Cardiol Intv 2016;9:825-7.
101. Bauer T, Linke A, Sievert H, et al. Comparison of the effectiveness of transcatheter aortic valve implantation in patients with stenotic bicuspid versus tricuspid aortic valves (from the German TAVI Registry). Am J Cardiol 2014;113:518-21.
102. Blackman DJ, Bleiziffer S, Gerckens U, et al. Safety and efficacy of a fully repositionable and retrievable transcatheter heart valve in patients with bicuspid aortic valve stenosis: an analysis from the RESPOND study. EuroPCR. Paris 2016.
103. Sievers HH, Schmidtke C. A classification system for the bicuspid aortic valve from 304 surgical specimens. J Thorac Cardiovasc Surg 2007;133:1226-33.
104. Van Mieghem NM, Blackman DJ, Hildick-Smith D, et al. Transcatheter aortic valve replacement using the Lotus valve with DepthGuard: first report from the RESPOND Extension study. CRT. Washington, D.C. 2017.
105. Pibarot P, Hahn RT, Weissman NJ, Monaghan MJ. Assessment of paravalvular regurgitation following TAVR: a proposal of unifying grading scheme. J Am Coll Cardiol Img 2015;8:340-60.
106. Herrmann HC, Thourani VH, Kodali SK, et al. One-year clinical outcomes with SAPIEN 3 transcatheter aortic valve replacement in high-risk and inoperable patients with severe aortic stenosis. Circulation 2016;134:130-40.
107. Escárcega RO, Magalhaes MA, Lipinski MJ, et al. Mortality in patients requiring pacemaker implantation following transcatheter aortic valve replacement: Insights from a systematic review and meta-analysis. Int J Cardiol 2014;174:207-8.
108. Mohananey D, Jobanputra Y, Kumar A, et al. Clinical and echocardiographic outcomes following permanent pacemaker implantation after transcatheter aortic valve replacement: Meta-analysis and meta-regression. Circ Cardiovasc Interv 2017;10:e005046.
109. Chakravarty T, Søndergaard L, Friedman J, et al. Subclinical leaflet thrombosis in surgical and transcatheter bioprosthetic aortic valves: an observational study. Lancet 2017;389:2383-92.
110. Jose J, Sulimov DS, El-Mawardy M, et al. Clinical bioprosthetic heart valve thrombosis after transcatheter aortic valve replacement: incidence, characteristics, and treatment outcomes. J Am Coll Cardiol Intv 2017;10:686-97.
111. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology

needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 2004;8:R204-12.

112. Mehta RL, Kellum JA, Shah SV, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care 2007;11:R31.
113. Saito S. REPRISE Japan: A prospective clinical investigation of a novel transcatheter aortic valve implantation system in Japan. Cardiovascular Intervention and Therapeutics. Kyoto, Japan 2017.
114. Saito S. One-year results from REPRISE Japan: A prospective clinical investigation of a novel transcatheter aortic valve implantation system in Japan. PCR Tokyo Valves, Tokyo 2018.
115. Meredith I, Walters D, Gooley R, et al. Primary endpoint results of the REPRISE NG Delivery System (DS) First Human Use study: Percutaneous aortic valve implantation with the next generation of fully repositionable and retrievable aortic valve. EuroPCR. Paris 2015.
116. Walters DL, Gooley R, Raffel C, et al. First report of clinical outcomes with the next-generation LOTUS Edge Valve System: Results from the LOTUS Edge Feasibility Trial. ACC. Washington, D.C. 2017.
117. Cesari M, Kritchevsky SB, Penninx BW, et al. Prognostic value of usual gait speed in well-functioning older people--results from the Health, Aging and Body Composition Study. J Am Geriatr Soc 2005;53:1675-80.
118. Green CP, Porter CB, Bresnahan DR, Spertus JA. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. J Am Coll Cardiol 2000;35:1245-55.
119. Ware JE, Kosinski M, Keller SD. A 12-item Short-Form Health Survey: Construction of scales and preliminary test of reliability and validity. Medical Care 1996;34:220-6.
120. Epstein AE, DiMarco JP, Ellenbogen KA, et al. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2013;61:e6-75.
121. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC Guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. J Am Coll Cardiol 2014;63:e57-185.
122. Robinson TN, Eiseman B, Wallace JI, et al. Redefining geriatric preoperative assessment using frailty, disability and co-morbidity. Ann Surg 2009;250:449-55.
123. Afilalo J, Mottillo S, Eisenberg MJ, et al. Addition of frailty and disability to cardiac surgery risk scores identifies elderly patients at high risk of mortality or major morbidity. Circ Cardiovasc Qual Outcomes 2012;5:222-8.

124. Afilalo J, Eisenberg MJ, Morin JF, et al. Gait speed as an incremental predictor of mortality and major morbidity in elderly patients undergoing cardiac surgery. J Am Coll Cardiol 2010;56:1668-76.

125. Studenski S, Perera S, Patel K, et al. Gait speed and survival in older adults. JAMA 2011;305:50-8.

126. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol Med Sci 2001;56A:M146-56.

127. Katz S, Downs TD, Cash HR, Grotz RC. Progress in development of the index of ADL. Gerontologist 1970;10:20-30.

128. Blanke P, Weir-McCall JR, Achenbach S, et al. Computed tomography imaging in the context of transcatheter aortic valve implantation (TAVI)/transcatheter aortic valve replacement (TAVR): an expert consensus document of the Society of Cardiovascular Computed Tomography. J Am Coll Cardiol Img 2019;12:1-24.

129. De Backer O, Dangas GD, Jilaihawi H, et al. Reduced leaflet motion after transcatheter aortic-valve replacement. N Engl J Med 2020;382:130-9.

130. Pache G, Schoechlin S, Blanke P, et al. Early hypo-attenuated leaflet thickening in balloon-expandable transcatheter aortic heart valves. Eur Heart J 2016;37:2263-71.

131. Søndergaard L, De Backer O, Kofoed KF, et al. Natural history of subclinical leaflet thrombosis affecting motion in bioprosthetic aortic valves. Eur Heart J 2017;38:2201-7.

132. Hansson NC, Grove EL, Andersen HR, et al. Transcatheter aortic valve thrombosis: incidence, predisposing factors, and clinical implications. J Am Coll Cardiol 2016;68:2059-69.

133. Ruile P, Jander N, Blanke P, et al. Course of early subclinical leaflet thrombosis after transcatheter aortic valve implantation with or without oral anticoagulation. Clin Res Cardiol 2017;106:85-95.

134. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation 2011;123:2736-47.

135. Ndrepepa G, Schuster T, Hadamitzky M, et al. Validation of the Bleeding Academic Research Consortium definition of bleeding in patients with coronary artery disease undergoing percutaneous coronary intervention. Circulation 2012;125:1424-31.

136. Durack DT, Lukes AS, Bright DK. New criteria for diagnosis of infective endocarditis: utilization of specific echocardiographic findings. Duke Endocarditis Service. Am J Med 1994;96:200-9.

137. Thygesen K, Alpert JS, White HD. Universal definition of myocardial infarction. Eur Heart J 2007;28:2525-38.

138. Sharp AS, Michev I, Maisano F, et al. A new technique for vascular access management in transcatheter aortic valve implantation. Catheter Cardiovasc Interv 2010;75:784-93.

139. Généreux P, Kodali S, Leon MB, et al. Clinical outcomes using a new crossover balloon occlusion technique for percutaneous closure after transfemoral aortic valve implantation. J Am Coll Cardiol Intv 2011;4:861-7.

25. Abbreviations and Definitions

25.1. *Abbreviations*

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

Table 25.1-1: Abbreviations and Acronyms

Abbreviation/Acronym	Definition
ADE	adverse device effect
AE	adverse event
AKIN	Acute Kidney Injury Network
AR	aortic regurgitation
AS	aortic stenosis
AV	atrioventricular
AVA	aortic valve area
AVR	aortic valve replacement
BARC	Bleeding Academic Research Consortium
BAV	balloon aortic valvuloplasty
BMI	body mass index
BSA	body surface area
BSC	Boston Scientific Corporation
CAD	coronary artery disease
CBC	complete blood count
CEC	Clinical Events Committee
CK	creatine kinase
CK-MB	creatine kinase-myoglobin band, a fraction of creatine kinase
CRC	Case Review Committee
CT	computed tomography
CVA	cerebrovascular accident
DVI	Doppler velocity index
ECG	electrocardiogram
eCRF	electronic case report form
EOA	effective orifice area
GCP	Good Clinical Practices
GDPR	General Data Protection Regulation
HALT	hypoattenuated leaflet thickening

Table 25.1-1: Abbreviations and Acronyms

Abbreviation/Acronym	Definition
HCP	Health care personnel
HREC	Human Research Ethics Committee
IB	Investigator Brochure
ICF	Informed Consent form
ICH	International Conference on Harmonisation
iEOA	indexed effective orifice area
IFU	Instructions for Use
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISO	International Organization for Standardization
ITT	intention-to-treat
LBBB	left bundle branch block
LV	left ventricle
LVEF	left ventricular ejection fraction
MACCE	major adverse cardiovascular and cerebrovascular events
MI	myocardial infarction
MRI	magnetic resonance imaging
mRS	Modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
NYHA	New York Heart Association
OAC	oral anticoagulant
PPM	permanent pacemaker
QOL	quality of life
RLM	reduced leaflet motion
SADE	serious adverse device effect
SAE	serious adverse event
SAP	statistical analysis plan
SAVR	surgical aortic valve replacement
TAVI/TAVR	transcatheter aortic valve implantation/replacement
TEE	transesophageal Doppler echocardiography
TIA	transient ischemic attack
TTE	transthoracic Doppler echocardiography
UADE	unanticipated adverse device effect
URL	upper reference limit (defined as 99th percentile of normal reference range)
VARC	Valve Academic Research Consortium

25.2. *Definitions*

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

Table 25.2-1: Definitions

Term	Definition
ACUTE KIDNEY INJURY (AKI) (AKIN System[111,112])	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:*** Subjects receiving renal replacement therapy are considered to meet Stage 3 criteria irrespective of other criteria.
ACUTE VESSEL OCCLUSION	The state of complete luminal obstruction with no antegrade blood flow
ADVERSE EVENT (AE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Any untoward medical occurrence, unintended disease or injury or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device. ***Note:*** This definition includes events related to the investigational medical device or the comparator. ***Note:*** This definition includes events related to the procedures involved. ***Note:*** For users or other persons, this definition is restricted to events related to investigational medical devices.
ADVERSE EVENT BECOME AWARE DATE	The become aware date for an adverse 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.
ADVERSE DEVICE EFFECT (ADE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Adverse event related to the use of an investigational medical device ***Note:*** 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:*** This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.
AORTIC DISSECTION	Intimal tear resulting in blood splitting the aortic media and producing a false lumen that can progress in an antegrade or retrograde direction Aortic dissection is further classified using Stanford classification (Types A and B depending on whether ascending or descending aorta involved) or DeBakey classification (Types I, II and III) [see Figure below].

Table 25.2-1: Definitions

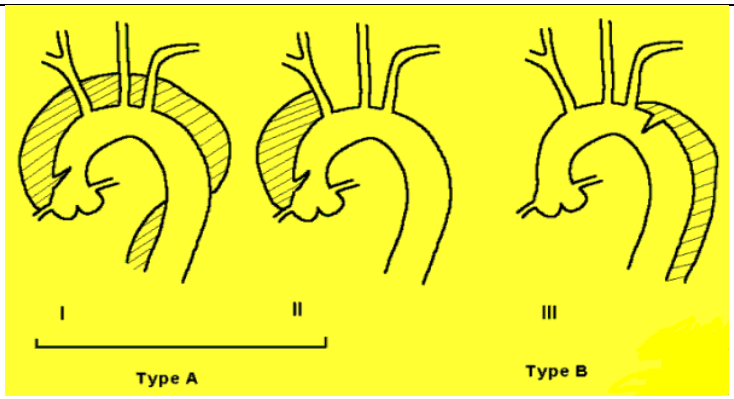
Term	Definition
	
AORTIC REGURGITATION (AR)	The leaking of the aortic valve that causes blood to flow in the reverse direction during ventricular diastole, from the aorta into the left ventricle. The echocardiographic findings in severe aortic regurgitation include the following. • An AR color jet dimension >60% of the left ventricular outflow tract diameter (may not be true if the jet is eccentric) • The pressure half-time of the regurgitant jet is <250 msec • Early termination of the mitral inflow (due to increase in LV pressure due to the AR) • Early diastolic flow reversal in the descending aorta. • Regurgitant volume >60 mL • Regurgitant fraction >55%
ARRHYTHMIA	Any variation from the normal rhythm of the heartbeat, including sinus arrhythmia, premature beat, heart block, atrial fibrillation, atrial flutter and tachycardia. Complete heart block, ventricular tachycardia and ventricular fibrillation are considered major arrhythmias. Data should be collected on any new arrhythmia resulting in hemodynamic instability or requiring therapy (therapy includes electrical/medical cardioversion or initiation of a new medication [oral anticoagulation, rhythm or rate controlling therapy]). New onset atrial fibrillation or atrial flutter (AF) is diagnosed as any arrhythmia within hospitalization that has the ECG characteristics of AF and lasts sufficiently long to be recorded on a 12-lead ECG, or at least 30 seconds on a rhythm strip. The therapeutic approach to new-onset AF (spontaneous conversion, electrical or medical cardioversion, initiation of oral anticoagulation, and rate or rhythm control medications) and any clinical consequences should be documented. ***Note:*** See also definitions for conductance disturbance and permanent pacemaker.
BLEEDING[61,62]	<u>Life-threatening or Disabling Bleeding</u> • Fatal bleeding (Bleeding Academic Research Consortium [BARC] type 5[134,135]) • Bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome (BARC type 3b and 3c)

Table 25.2-1: Definitions

Term	Definition
	• 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.
CLINICAL PROCEDURAL SUCCESS (IN-HOSPITAL)	Implantation of the device in the absence of death, disabling stroke, major vascular complications, and life-threatening or major bleeding
CONDUCTION DISTURBANCES[61,62]	Implant-related new or worsened cardiac conduction disturbances include new or worsened first degree atrioventricular (AV) block, second degree AV block (Mobitz I or Mobitz II), third degree AV block, incomplete right bundle branch block (RBBB), RBBB, intraventricular conduction delay, left bundle branch block (LBBB), left anterior fascicular block, or left posterior fascicular block, including block requiring permanent pacemaker implant ***Note:*** High grade AV block is considered persistent if it is present every time the underlying rhythm is checked. ***Note:*** 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

Table 25.2-1: Definitions

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

Table 25.2-1: Definitions

Term	Definition
	available data from the Bureau of the Census, the geographic unit formed by combining all ZIP codes with the same three initial digits contains more than 20,000 people and/or the initial three digits of a ZIP code for all such geographic units containing 20,000 or fewer people is changed to 000 • All elements of dates (except year) for dates that are directly related to an individual, including birth date, admission date, discharge date, death date, and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older • Telephone numbers • Fax numbers • Device identifiers and serial numbers • E-mail addresses • Web Universal Resource Locators (URLs) • Internet Protocol (IP) addresses • Medical record numbers • Biometric identifiers, including finger and voice prints • Health plan beneficiary numbers • Full-face photographs and any comparable images Any other unique identifying number, characteristic, or code (including subject ID number)
DEATH	<u>All-cause Death</u> Death from any cause after a valve intervention. <u>Cardiovascular Death</u> Any one of the following criteria is met. • Any death due to proximate cardiac cause (e.g., myocardial infarction, cardiac tamponade, worsening heart failure) • Sudden or unwitnessed death • Death of unknown cause • Death caused by noncoronary vascular conditions such as neurological events, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular disease • All procedure-related deaths, including those related to a complication of the procedure or treatment for a complication of the procedure • All valve-related deaths including structural or nonstructural valve dysfunction or other valve-related adverse events <u>Non-cardiovascular Death</u> • Any death in which the primary cause of death is clearly related to another condition (e.g. trauma, cancer, suicide)
DEVICE DEFICIENCY *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Any inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety or performance. ***Note:*** Device deficiencies may include malfunctions, use errors, or inadequacy in the information supplied by the manufacturer.
DEVICE FAILURE	A device failure is identified whenever the criteria for device success are not met.

Table 25.2-1: 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 (VARC 2[70] definition)	Absence of procedural mortality, correct positioning of a single valve into the proper anatomical location, and intended performance of the study device (indexed effective orifice area [iEOA] >0.85 cm^2/m^2 for BMI <30 kg/cm^2 and iEOA >0.70 cm^2/m^2 for BMI ≥30 kg/cm^2 plus either a mean aortic valve gradient <20 mmHg or a peak velocity <3m/sec, and no 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[136] and necessitates the following. • Two major criteria -OR- • One major and three minor criteria -OR- • Five minor criteria <u>Major Criteria</u> • Positive blood culture for infective endocarditis o Typical microorganism consistent with infective endocarditis from 2 separate blood cultures, as noted below. ▪ Viridans streptococci, *Streptococcus bovis*, or HACEK group (*Haemophilus* [*Haemophilus parainfluenzae, Haemophilus aphrophilus, and Haemophilus paraphrophilus*], *Actinobacillus actinomycetemcomitans* [*Aggregatibacter actinomycetemcomitans*], *Cardiobacterium hominis, Eikenella corrodens, Kingella kingae* -OR- ▪ Community-acquired *Staphylococcus aureus* or enterococci, in the absence of a primary focus -OR- o Microorganisms consistent with infective endocarditis from persistently positive blood cultures defined as noted below. ▪ Two (2) positive cultures of blood samples drawn >12 hours apart -OR- ▪ All of 3 or a majority of 4 separate cultures of blood (with first and last sample drawn 1 hour apart) • Evidence of endocardial involvement o Positive echocardiogram for infective endocarditis defined as noted below.

Table 25.2-1: Definitions

Term	Definition
	▪ 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.
GENERAL DATA PROTECTION REGULATION	The General Data Protection Regulation (GDPR) is a legal framework that sets guidelines for the collection and processing of personal information of individuals within the European Union.
HEMOLYSIS	Two plasma free hemoglobin values >40 mg/dL with the two readings taken within a single 48-hour period. If the second plasma free hemoglobin assessment is not performed within 48 hours following an initial determination of >40 mg/dL, this would qualify as an AE.
HOSTILE CHEST	Any of the following or other reasons that make redo operation through sternotomy or right anterior thoracotomy prohibitively hazardous: • Abnormal chest wall anatomy due to severe kyphoscoliosis or other skeletal abnormalities (including thoracoplasty, Potts' disease) • Complications from prior surgery • Evidence of severe radiation damage (e.g. skin burns, bone destruction, muscle loss, lung fibrosis or esophageal stricture)

Table 25.2-1: Definitions

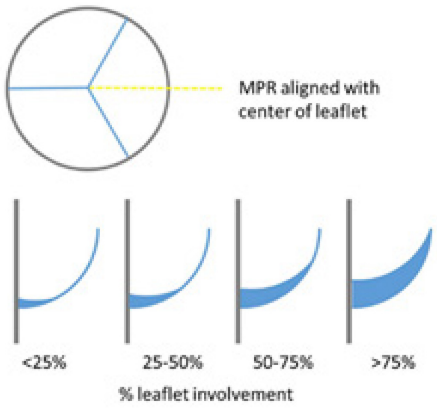
Term	Definition
	• History of multiple recurrent pleural effusions causing internal adhesions
HYPO-ATTENUATED LEAFLET THICKENING (HALT)[128]	Hypo-attenuated leaflet thickening (HALT) is defined as visually identifiable increased leaflet thickness on contrast-enhanced multi-planar reformats, carefully aligned with the long and short axis of the valve prosthesis. The extent of HALT is classified as follows:  The dashed yellow line indicates the orientation of the long axis views in the lower row, aligned with the center of the cusps. The extent of leaflet thickening can be graded on a subjective 4-tier grading scale along the curvilinear orientation of the leaflet. Typically, hypo-attenuated leaflet thickening appears meniscal-shaped on long axis reformats, with greater thickness at the base than towards the center of the leaflet.
IMPLANTED ANALYSIS SET	This population includes all subjects who sign an Informed Consent Form, are enrolled in the trial, and are implanted with the assigned, randomized study device. ***Note:*** If a subject receives 2 valves, the subject is assigned to the group corresponding to the first valve received.
INTENT TO TREAT (ITT) ANALYSIS SET	This population includes all subjects who sign an Informed Consent Form, are enrolled in the trial, and are randomized, whether or not an assigned study device is implanted. Subjects in the ITT population will be followed with their ITT cohort. ***Note:*** If a subject receives 2 valves, the subject is assigned to the group corresponding to the first valve received.
INTERNAL MAMMARY ARTERY OR OTHER CRITICAL CONDUIT(S) CROSSING MIDLINE AND/OR ADHERENT TO POSTERIOR TABLE OF STERNUM	A patent IMA graft that is adherent to the sternum such that injuring it during reoperation is likely. A patient may be considered extreme risk if any of the following are present: • The conduit(s) are radiographically indistinguishable from the posterior table of the sternum. • The conduit(s) are radiographically distinguishable from the posterior table of the sternum but lie within 2-3mm of the posterior table.
INTRACRANIAL HEMORRHAGE	Collection of blood between the brain and skull; subcategorized as epidural, subdural, and subarachnoid bleeds.

Table 25.2-1: Definitions

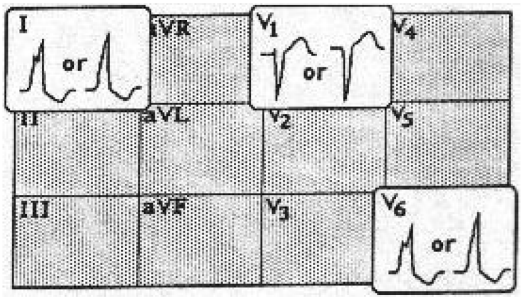
Term	Definition
LEFT BUNDLE BRANCH BLOCK (LBBB)	The appearance of typical complete LBBB in the three KEY leads (I, V1, and V6) with the following diagnostic criteria [see Figure below]. • The heart rhythm must be supraventricular in origin • QRS widening to at least 0.12 sec • An upright (monophasic)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

Table 25.2-1: Definitions

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

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

Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST-segment elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/ or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.
Pathological findings of an acute myocardial infarction[137].

</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-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

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

Table 25.2-1: Definitions

Term	Definition
OPERATIVE RISK	Operative risk is determined by a center cardiac surgeon and must be confirmed by the Case Review Committee (including a cardiac surgeon). **Intermediate**: Estimated 30-day risk of mortality is 3–10% **High**: Estimated 30-day risk of mortality is >10–15%% **Very High**: Estimated 30-day risk of mortality is >15% **Extreme**: Estimated 30-day risk of irreversible morbidity or mortality is ≥50%
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[120]	Implantation of new PPM after the index procedure resulting from new or worsened conduction disturbances • 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.
REDUCED LEAFLET MOBILITY/MOTION (RLM)[129]	Systolic leaflet excursion/motion is classified as: • Grade 0: normal/unrestricted; • Grade 1: partially restricted – limited to base; • Grade 2: mildly restricted – involving more than the base, but less than 50% of the leaflet along curvilinear dimensions; • Grade 3: moderately restricted – involving more than 50% but less than 75% of the leaflet along curvilinear dimensions; Grade 4: largely immobile. Quantitative assessment of leaflet motion is performed with a blood pool inversion volume rendered cine reconstruction throughout the cardiac cycle evaluating the bioprosthetic leaflets.
REPEAT PROCEDURE FOR VALVE-RELATED DYSFUNCTION	Any surgical or percutaneous interventional catheter procedure that repairs, otherwise alters or adjusts, or replaces a previously implanted valve. In addition to surgical re-operations, balloon dilatation, interventional manipulation, repositioning, or retrieval, and other catheter-based interventions for valve-related complications are also considered re-interventions. Cardiac re-interventions will be categorized as repeat TAVR, valvuloplasty, or surgical AVR.
REPOSITIONING OF A VALVE	Any movement of the valve after the lead in phase (after the posts have entered the buckles)

Table 25.2-1: Definitions

Term	Definition
RESHEATHING OF A VALVE	Full resheathing occurs when the tops of the posts re-enter the Lotus catheter during repositioning. Partial resheathing occurs when the posts do not re-enter the Lotus catheter during repositioning.
RESPIRATORY INSUFFICIENCY	Inadequate ventilation or oxygenation
RESPIRATORY FAILURE	The need for ventilatory support for >72 hours associated with an inability to wean from the respirator for any reason.
RIGHT VENTRICULAR INSUFFICIENCY	• Defined as sequelae of right ventricular failure including the following. o Significantly decreased right ventricular systolic and/or diastolic function o Tricuspid valvular regurgitation secondary to elevated pressure • Clinical symptoms to include the following. o Hepatic congestion o Ascites 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.
SAFETY ANALYSIS SET	This population includes all subjects in the ITT analysis set who have a study device implanted, regardless of the assigned treatment group.
SERIOUS ADVERSE EVENT (SAE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	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 hospitalization or prolongation of existing hospitalization, or o medical or surgical intervention to prevent life- threatening illness • Led to fetal distress, fetal death or a congenital abnormality or birth defect ***Note:*** Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered a serious adverse event.
SERIOUS ADVERSE DEVICE EFFECT (SADE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event
SOURCE DATA (per ISO 14155)	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)	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.

Table 25.2-1: Definitions

Term	Definition
	Note: If thermal paper from a device programmer is to be used for source documentation, signed and dated photocopies or printed portable document format files should be used instead or the strips should be electronically saved.
STROKE[61,62]	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:*** The CEC will adjudicate ischemic versus hemorrhagic stroke. ***Note:*** A stroke may be classified as undetermined if there is insufficient information to allow categorization as ischemic or hemorrhagic **Stroke Diagnostic Criteria** • Rapid onset of a focal or global neurological deficit with at least one of the following: change in level of consciousness, hemiplegia, hemiparesis, numbness or sensory loss affecting one side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke • Duration of a focal or global neurological deficit ≥24 h; OR <24 h, if available neuroimaging documents a new hemorrhage or infarct; OR the neurological deficit results in death • No other readily identifiable nonstroke cause for the clinical presentation (e.g., brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences), to be determined by or in conjunction with designated neurologist • Confirmation of the diagnosis by at least one of the following. o Neurology or neurosurgical specialist o Neuroimaging procedure (MRI or CT scan), but stroke may be diagnosed on clinical grounds alone ***Note:*** 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:*** Modified Rankin Scale assessments should be made by a neurology professional or by qualified individuals according to a certification process. ***Note:*** 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.

Table 25.2-1: Definitions

Term	Definition
TAV-IN-TAV DEPLOYMENT	An additional valve prosthesis is implanted within a previously implanted prosthesis because of suboptimal device position and/or function during or after the index procedure.
TRANSIENT ISCHEMIC ATTACK (TIA)	• Transient episode of focal neurological dysfunction caused by brain, spinal cord, or retinal ischemia, without acute infarction • Duration of a focal or global neurological deficit is <24 h • Neuroimaging does not demonstrate a new hemorrhage or infarct (if performed) ***Note:*** The difference between TIA and ischemic stroke is the presence of tissue damage or new sensory-motor deficit persisting >24 hours. By definition, TIA does not produce lasting disability.
UNANTICIPATED ADVERSE DEVICE EFFECT *Ref: 21CFR Part 812* (UADE)	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the protocol or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.
UNPLANNED USE OF CARDIOPUL-MONARY BYPASS	Unplanned use of cardiopulmonary bypass 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 MALPOSITIONING	Includes valve migration, valve embolization, or ectopic valve 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.

Table 25.2-1: Definitions

Term	Definition
VASCULAR ACCESS SITE AND ACCESS RELATED COMPLICATIONS	**Major Vascular Complications** • Any aortic dissection, aortic rupture, annulus rupture, left ventricle perforation, or new apical aneurysm/pseudoaneurysm • Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, hematoma, irreversible nerve injury, compartment syndrome, percutaneous closure device failure*) ***leading to*** death, life-threatening or major bleeding**, visceral ischaemia, or neurological impairment • Distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage • The use of unplanned endovascular or surgical intervention ***associated*** with death, major bleeding, visceral ischaemia or neurological impairment • Any new ipsilateral lower extremity ischemia documented by patient symptoms, physical exam, and/or decreased or absent blood flow on lower extremity angiogram • Surgery for access site-related nerve injury • Permanent access site-related nerve injury **Minor Vascular Complications** • Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysms, hematomas, percutaneous closure device failure*) not leading to death, life-threatening or major bleeding**, visceral ischaemia or neurological impairment • Distal embolization treated with embolectomy and/or thrombectomy and not resulting in amputation or irreversible end-organ damage • Any unplanned endovascular stenting or unplanned surgical intervention not meeting the criteria for a major vascular complication • Vascular repair or the need for vascular repair (via surgery, ultrasound-guided compression, transcatheter embolization, or stent-graft) ***Percutaneous Closure Device Failure** Failure of a closure device to achieve hemostasis at the arteriotomy site leading to alternative treatment (other than manual compression or adjunctive endovascular ballooning) ***Note:*** Pre-planned surgical access or a planned endovascular approach to vascular closure (e.g., "pre-closure")[138,139] 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:*** 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[61,62]
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

Table 25.2-1: Definitions

Term	Definition

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; GDPR= General Data Protection Regulation; 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; TAV=transcatheter aortic valve; TAVR=transcatheter aortic valve replacement; TEE=transesophageal Doppler echocardiography; TIA=transient ischemic attack; URL=upper reference limit (defined as 99th percentile of normal reference range); VARC=Valve Academic Research Consortium

26. Revision History

26.1. *Summary of Protocol Revision History*

Protocol revision history is provided in **Table 26.1-1.**

Table 26.1-1: Protocol Revision History

<table>
<tr><th>Revision Version</th><th>Protocol Date</th><th>Template Number and Version</th><th>Protocol Sections Modified</th><th>Summary of Changes</th><th>Justification for Changes</th></tr>
<tr><td>A</td><td>16-Nov-2016</td><td>90702637 Rev/Ver AG</td><td>–</td><td>Not applicable.</td><td>–</td></tr>
<tr><td rowspan="6">B</td><td rowspan="6">15-Feb-2017</td><td rowspan="6">90702637 Rev/Ver AG</td><td>Page 2</td><td>Current Version: 15-Feb-2017
Updated Table of Revision History</td><td>Updated for clarity</td></tr>
<tr><td>2, Protocol Synopsis - Planned Number of Subjects/ Investigational Centers/ Countries</td><td>Subjects will be enrolled at up to 45 centers in the United States. There will be up to 840 subjects in REPRISE IV as shown below.<table><tr><td>Cohort</td><td>Number of Subjects</td></tr><tr><td>Randomized</td><td>620</td></tr><tr><td>Roll-In</td><td>Up to 120</td></tr><tr><td>Bicuspid Nested Registry</td><td>100</td></tr></table></td><td>Increase of number of subjects in the Bicuspid Nested Registry</td></tr>
<tr><td>2, Protocol Synopsis – Exclusion Criteria</td><td>EC16. Subject has any therapeutic invasive cardiac procedure resulting in a permanent implant that is performed within 30 days prior to the index procedure (unless part of planned strategy for treatment of concomitant coronary artery disease and except for pacemaker or implantable cardioverter defibrillator implantation which are allowed).</td><td>Updated for clarity</td></tr>
<tr><td>8.1 Scale and Duration</td><td>Updated Figure 8.1-1: REPRISE IV Study Design</td><td>Increase of number of subjects in the Bicuspid Nested Registry</td></tr>
<tr><td>8.3 Study Design Justification</td><td>There will be up to 840 subjects in REPRISE IV. In order to support the stated objectives of this study (see Section 6) while also limiting the potential exposure of study subjects to risk, up to 120 subjects will be enrolled in the roll-in phase of this study (at centers without previous LOTUS Edge Valve experience), 620 subjects will be randomized and enrolled, and 100 subjects will be enrolled in the Bicuspid Nested Registry.</td><td>Increase of number of subjects in the Bicuspid Nested Registry</td></tr>
<tr><td>9.3 Exclusion Criteria</td><td>EC16. Subject has any therapeutic invasive cardiac procedure resulting in a permanent implant that is performed within 30 days prior to the index procedure (unless part of planned strategy for treatment of concomitant coronary artery disease and except for pacemaker or implantable cardioverter defibrillator implantation which are allowed).</td><td>Updated for clarity</td></tr>
</table>

Table 26.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
			11.1 Data Collection	Updated Figure 11.1-1: REPRISE IV Data Collection Scheme Updated Table 11.1-1: Study Event Schedule	Updated for clarity and to include CT assessment at 30 days for subjects enrolled in the Bicuspid Nested Registry. Increase of number of subjects in the Bicuspid Nested Registry
			11.10.1 30-Day Follow-up (30±7 Days)	All enrolled subjects… • Complete adverse event (AE, SAE, SADE, UADE, ADE and CEC events) … with associated treatment • For subjects in the Bicuspid Nested Registry, a computed tomography scan at 30 days post LOTUS Edge Valve implantation.	Updated for clarity and to include CT assessment at 30 days for subjects enrolled in the Bicuspid Nested Registry.
			27 Appendices	Added Section 27.1-1 and Table 27.1-1	Updated for clarity
C	23-Sep-2018	90702637 Rev/Ver AG	Page 1	Sponsor: Boston Scientific… USA Australian Representative Boston Scientific Pty. Ltd. Building 1, Level 6 191 O'Riordan Street Mascot, NSW 2020, Australia	Added for Australian study centers in REPRISE IV
			Page 2	Clinical Contacts Laoti Bussone Senior Clinical Trial Manager, Interventional Cardiology Boston Scientific Corporation 100 Boston Scientific Way, Marlborough, MA 01752 USA Arjun M. Bhat Clinical Trial Manager, Structural Heart – Interventional Cardiology Boston Scientific Corporation 100 Boston Scientific Way, Marlborough, MA 01752 USA	New project managers
				Study Coordinating Principal Investigators	New study coordinating principal investigators

Table 26.1-1: Protocol Revision History

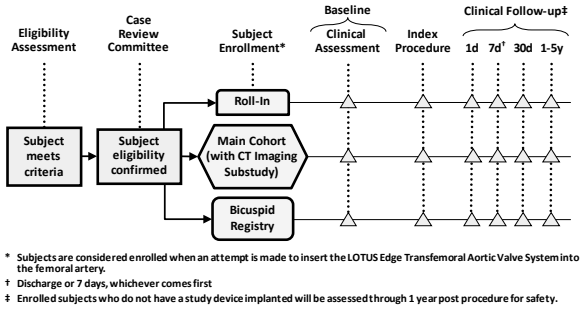
<table>
<tr><th>Revision Version</th><th>Protocol Date</th><th>Template Number and Version</th><th>Protocol Sections Modified</th><th>Summary of Changes</th><th>Justification for Changes</th></tr>
<tr><td rowspan="5"></td><td rowspan="5"></td><td rowspan="5"></td><td rowspan="2"></td><td>Interventional Cardiologist Study Co-Principal Investigator
Ted Feldman, MD
Evanston Hospital, North Shore University Health System
Cardiology Division - Walgreen Building 3rd Floor
2650 Ridge Avenue
Evanston, IL 60201 USA

Cardiac Surgeon Study Co-Principal Investigator
Vinod H. Thourani, MD
MedStar Heart & Vascular Institute
MedStar Washington Hospital Center
110 Irving St NW
Washington, DC 20010 USA</td><td></td></tr>
<tr><td>Current Version: 23-Sep-2018
Updated revision history table</td><td>Protocol revision</td></tr>
<tr><td>Section 2</td><td><table>
<tr><th>Device Name/Size</th><th>Description</th></tr>
<tr><td>LOTUS Edge…</td><td>Includes 2 main…
- a bioprosthetic…(similar to the Lotus…)
- a next…
…introduced percutaneously via the femoral artery.</td></tr>
<tr><td>~~iSleeve™ Introducer Set~~
~~14 and 15 French (F)~~</td><td>~~- a dilator... arteries ≥5.5 mm with the 14F sheath (to deliver the 23mm LOTUS Edge valve) and ≥5.9 mm with the 15F sheath…~~</td></tr>
<tr><td colspan="2">The iSleeve™ Introducer Set (iSleeve) and the large Lotus Introducer Set (LIS-L) can be used as accessories to facilitate vascular introduction and deployment of the LOTUS Edge Valve System (23mm, 25mm, or 27mm valve sizes). The iSleeve has an expandable sheath component and a dilator enabling access to transfemoral arteries ≥5.9 mm. The LIS-L is intended for use in subjects with femoral vascular access ≥6.5 mm. In countries where the introducer sets are approved, the commercial devices</td></tr>
</table></td><td>Updated for clarity to reflect use of commercial introducer sets.</td></tr>
</table>

Table 26.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				will be used. In countries where they are not approved, they will be considered investigational devices.	
				Comparator For the primary endpoint, a performance goal (PG) based on 1-year TAVR outcomes derived from published literature will be used as the comparator for analysis.	Updated study design to single arm
			Section 2 Study Design	REPRISE IV is a prospective, multicenter single-arm study designed… subjects who have severe native aortic stenosis… Study cohorts include the following. - **Main Cohort**: A prospective, multicenter, single-arm cohort of subjects with severe aortic stenosis who are considered at intermediate risk for surgical aortic valve replacement and are treated with the LOTUS Edge Valve System. o **CT Imaging Substudy:** Selected centers with the ability to perform high quality 4D computed tomography (CT) scans will include subjects from the Main Cohort in a CT imaging substudy to assess the prevalence of reduced leaflet mobility and its relationship, if any, to clinical events. - **Bicuspid Nested Registry**: A prospective, single-arm, nested registry cohort of subjects who have a native bicuspid aortic valve and are considered at intermediate risk for surgical aortic valve replacement and are treated with the LOTUS Edge Valve System. - **Roll-In Cohort**: A roll-in phase with the study device for centers that do not have implantation…evaluable Main Cohort and Bicuspid Nested Registry. Data from roll-in subjects will be summarized separately from the evaluable Main Cohort … The REPRISE IV study will be conducted in accordance with 21 CFR Parts 11, 50, and 54; the relevant parts of the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practices (GCP); or the International Standard ISO 14155 Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice; ethical principles that have their origins in the Declaration of Helsinki; and pertinent individual country/state/local laws and regulations. The study shall not begin until the required approval/favorable opinion from the Institutional	Addition of a CT Imaging Substudy. Text updated for clarity (including addition of a new study design overview figure)

Table 26.1-1: Protocol Revision History

<table>
<tr><th>Revision Version</th><th>Protocol Date</th><th>Template Number and Version</th><th>Protocol Sections Modified</th><th>Summary of Changes</th><th>Justification for Changes</th></tr>
<tr><td></td><td></td><td></td><td></td><td>Review Board/Human Research Ethics Committee (IRB/HREC) and/or regulatory authority has been obtained, if appropriate.
The study design is summarized in the figure below.
 

REPRISE IV Study Design Overview</td><td></td></tr>
<tr><td></td><td></td><td></td><td>Section 2
Planned Number of Subjects/ Investigational Centers/ Countries</td><td>Subjects will be enrolled at up to 50 centers in the United States and Australia. There will be up to 896 subjects enrolled in REPRISE IV as shown below.
<table>
<tr><th>Cohort</th><th>Number of Subjects</th></tr>
<tr><td>Randomized</td><td>696*</td></tr>
<tr><td>Bicuspid Nested Registry</td><td>100</td></tr>
<tr><td>Roll-In</td><td>Up to 100</td></tr>
</table>
* Up to 200 subjects from the main cohort will be enrolled in the CT Imaging Substudy. If 200 subjects have not enrolled in the CT Imaging Substudy by completion of enrollment in the main cohort, additional subjects who meet the REPRISE IV eligibility criteria will be enrolled in a separate CT Imaging Cohort to achieve a total of 200 subjects in the CT Imaging Substudy.</td><td>Updated study design (including addition of a CT Imaging Substudy) and addition of Australian investigative centers.</td></tr>
<tr><td></td><td></td><td></td><td>Section 2 Primary Endpoint</td><td>Composite of all-cause mortality and all stroke at 1 year</td><td>Updated study design</td></tr>
</table>

Table 26.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
			Section 2 Secondary Endpoint	No powered secondary endpoint	Updated study design
			Section 2 Additional Measurements	Additional measurements… will be collected peri- and post-procedure, at discharge or 7 days post-procedure (whichever comes first), 30 days, ~~6 months,~~ and 1, 2, 3, 4, and 5 years post index procedure… -Neurological status as determined by the following: ~~o Neurological physical exam at discharge…~~ o National Institutes of Health Stroke Scale (NIHSS) and modified Rankin Scale (mRS) assessments, which must be performed at baseline and pre-specified timepoints for all enrolled subjects. NIHSS and mRS must be performed by a neurology professional or certified personnel. o For subjects diagnosed with a stroke, a neurological physical exam, mRS, and NIHSS must be performed after the event; mRS must also be administered at 90±14 days following a stroke; the simplified mRS questionnaire may be used for this follow-up assessment. The neurological physical exam must be conducted by a neurologist, neurology fellow, neurology physician assistant, or neurology nurse practitioner… - For subjects in the Bicuspid Nested Registry, a CT scan at 30 days post LOTUS Edge Valve implantation; the data will be evaluated by an independent CT core laboratory. - For subjects in the CT Imaging Substudy, a 4D CT scan at 30 days and at 1 year post LOTUS Edge valve implantation to assess the prevalence of reduced leaflet mobility and its relationship, if any, to clinical events. The data will be evaluated by an independent CT core laboratory. **Note 1**: For the LOTUS Edge valve, repositioning may be achieved with partial or full resheathing of the valve. **Note 2**: At least 1 echocardiogram must be obtained before discharge or 7 days (whichever comes first); if multiple echocardiographic studies are performed prior to discharge and within 7 days of the procedure, the latest study performed will be used for analysis.	Updated time points and measurements
			Section 2	**Main Cohort:** Subjects with severe aortic valve stenosis who meet all eligibility criteria may be treated with the LOTUS Edge Valve System.	Updated study design

Table 26.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
			Method of Assigning Subjects to Treatment	-Up to 200 subjects from the main cohort will be enrolled in the CT Imaging Substudy. If 200 subjects have not enrolled in the CT Imaging Substudy by completion of enrollment in the main cohort, additional subjects who meet the REPRISE IV eligibility criteria will be enrolled in a separate CT Imaging Cohort to achieve a total of 200 subjects in the CT Imaging Substudy **Bicuspid Nested Registry:** Subjects with a native bicuspid aortic valve who meet all inclusion criteria and have no other exclusion criterion may be treated with the LOTUS Edge Valve System as part of a single-arm, nested registry cohort. **Roll-In Cohort:** For centers that do not have implantation experience with the LOTUS Edge Valve System at least 2 roll-in subjects will be treated before commencing enrollment in the Main Cohort and Bicuspid Nested Registry.	
			Section 2 Follow-up Schedule	All subjects implanted with a study device will be assessed at baseline, peri- and post-procedure, at discharge or 7 days post-procedure (whichever comes first), 30 days, ~~6 months,~~ 1 year, and then annually for up to 5 years post-procedure. Subjects who are enrolled but not implanted with a study device at the time of the procedure will be followed for safety through 1 year. Visits are to be an office/clinical visit but may be done in-hospital should the subject be admitted at the time. Procedures at each scheduled visit are described above under "Additional Measurements."	Text updated for clarity
			Section 2 Study Duration	Subjects implanted with a study device will be followed for 5 years after the index procedure. Enrollment is expected to be completed in approximately 12 months; therefore, the total study duration is estimated to be approximately 6 years.	
			Section 2 Participant Duration	The study duration for each subject is expected to be approximately 5 years.	
			Section 2 Adjunctive Pharmacologic Therapy	**Anti-Platelet Therapy** Per society guidelines[b], antiplatelet therapy with aspirin and a $P2Y_{12}$ inhibitor (clopidogrel recommended) is recommended after TAVR to decrease the risk of thrombotic or thromboembolic complications if there are no contraindications to these medications.	Updated to reflect current therapy recommendations

Table 26.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				$P2Y_{12}$ Inhibitor (clopidogrel recommended) A loading dose of a $P2Y_{12}$ inhibitor (recommended dose of ≥300 mg for clopidogrel, 60 mg for prasugrel, 180 mg for ticagrelor) is required for subjects who have not been on $P2Y_{12}$ inhibitor therapy for ≥72 hours at the time of the index procedure. The loading dose must be administered prior to the implant procedure. After the valve implant procedure, a $P2Y_{12}$ inhibitor is required for at least 1 month (clopidogrel is recommended with a dose of 75 mg daily). **Note 3:** If a subject requires chronic anticoagulation, either a $P2Y_{12}$ inhibitor (clopidogrel recommended) or aspirin is required prior to and after the implant procedure in addition to the anticoagulant therapy (but both aspirin and a $P2Y_{12}$ inhibitor are not required). After the implant procedure, the subject must be treated with an oral anticoagulant (warfarin or another vitamin K antagonist recommended) and either a $P2Y_{12}$ inhibitor (clopidogrel recommended) or aspirin for at least 1 month. b: Holmes DR, et al. J Am Coll Cardiol. 2012;59:1200–1254 Nishimura R, et al. J Am Coll Cardiol. 2014;63: e57–e185 Nishimura R, et al. Circulation. 2017;135:e1159–e95	
			Section 2 Inclusion Criteria	IC2. A subject in the Bicuspid Aortic Valve Nested Registry cohort must have a documented Sievers Type 0~~2~~ or Sievers Type 1 bicuspid valve based on… IC3.Subject … Committee [CRC]) ~~and, for the randomized cohort, is deemed treatable with an available size of both test and control device~~. IC5. Heart team (which must include an experienced cardiac interventionalist and an experienced cardiac surgeon) agrees that the subject is at intermediate risk of operative mortality (≥3% and <8% at 30 days based on the Society of Thoracic Surgeons risk score and other clinical comorbidities unmeasured by the risk calculator) and TAVR is appropriate. IC6. Heart team ~~(which must include a cardiac interventionalist and an experienced cardiac surgeon)~~ agrees that the subject is likely to benefit from valve replacement.	Updated for clarity

Table 26.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				IC7. Subject (or legal representative) has been informed of the study requirements and the treatment procedures, and provides written informed consent. IC8. Subject, family member, and/or legal representative agree(s) and subject is capable of returning to the study hospital for all required scheduled follow up visits. IC9. Subject is expected to be able to take the protocol-required adjunctive pharmacologic therapy.	
			Section 2 Exclusion Criteria	EC1. Subject has a unicuspid or bicuspid aortic valve (not applicable to subjects in the Bicuspid Nested Registry cohort). **Note 6:** Subjects in the Bicuspid Nested Registry cohort will have a documented Sievers Type 02 or Sievers Type 1 bicuspid valve based on CT assessment and confirmed by the CT core lab. Subjects are not eligible for inclusion in the Bicuspid Nested Registry cohort if the maximum diameter of the ascending aorta is >45 mm or if the subject has another indication for aortic root replacement. Subjects with a Sievers Type 2 bicuspid valve are not eligible for enrollment in any study cohort. EC4. Subject is on renal replacement therapy or has GFR <20 (based on Cockcroft-Gault formula). EC7. Subject has moderate to severe mitral stenosis (mitral valve area ≤1.5 cm^2 and diastolic pressure half-time ≥150 ms, Stage C or D[c]). EC8. Subject has a need for emergency surgery for any reason. EC9. Subject has a history of endocarditis within 6 months of index procedure or evidence of an active systemic infection or sepsis. EC10. Subject has echocardiographic evidence of new intra-cardiac vegetation or intraventricular or paravalvular thrombus requiring intervention. EC11. Subject has platelet count <50,000 cells/mm^3 or >700,000 cells/mm^3, or white blood cell count <1,000 cells/mm^3. EC12. Subject has had a gastrointestinal bleed… EC16. Subject has any therapeutic invasive cardiac or vascular procedure within 30 days prior to the index procedure (except for	

Table 26.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				balloon aortic valvuloplasty or pacemaker or implantable cardioverter defibrillator implantation, which are allowed). EC20. Subject has arterial access that is not acceptable for the study device ~~(test or control)~~ delivery systems as defined in the device ~~(test or control)~~ Instructions For Use. EC22.Subject has current problems with substance abuse (e.g., alcohol, etc.) that may interfere with the subject's participation in this study. c: Nishimura RA, et al. J Am Coll Cardiol. 2014;63:e57–e185	
			Section 2 Additional Exclusion Criteria	Additional exclusion criteria apply to subjects considered for enrollment in the CT Imaging Substudy as listed below. AEC1. Subject has eGFR <30 mL/min (chronic kidney disease stage IV or stage V). AEC2. Subject has atrial fibrillation that cannot be rate controlled to ventricular response rate < 60 bpm. AEC3. Subject is expected to undergo chronic anticoagulation therapy after the index procedure. **Note 7:** Subjects treated with short-term anticoagulation post procedure can be included in the imaging substudy; in these subjects the 30-day imaging will be performed 30 days after discontinuation of anticoagulation.	Added for the CT Imaging Substudy
			Section 2 Analysis Sets	Analysis sets are listed below. - Intention-To-Treat (ITT): This population includes all subjects who sign an Informed Consent Form and are enrolled in the study ~~and are randomized~~, regardless of whether the study device is implanted. - Implanted: This population includes all subjects who sign an Informed Consent Form, are enrolled in the study, and are implanted with the ~~assigned, randomized~~ study device. A subject is considered enrolled in the study when an attempt is made to insert a LOTUS Edge Valve.	Updated study design
			Section 2 Primary Endpoint Statistical Hypothesis	In the Main Cohort, the rate of the primary endpoint (composite of all-cause mortality and all stroke at 1 year) is less than the performance goal (PG) of 15.2% (expected rate of 11.1% plus testing margin of 4.1%).	

Table 26.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
			Section 2 Statistical Test Method for the Primary Endpoint	A one-sample z test will be used to test the one-sided hypothesis that the 1-year composite primary endpoint rate for LOTUS Edge in the Main Cohort is less than the PG: H0: $P_{LOTUS\ Edge} \geq PG$ H1: $P_{LOTUS\ Edge} < PG$ where $P_{LOTUS\ Edge}$ is the primary endpoint rate for the LOTUS Edge group and PG is the performance goal. The primary analysis set for the primary endpoint is the ITT analysis set. This endpoint will also be analyzed for the implanted analysis set.	
			Section 2 Sample Size Parameters for the Primary Endpoint	The sample size calculation for the primary endpoint (composite of all-cause mortality and all stroke at 1 year) is based on the following assumptions. • Expected rate for LOTUS Edge = 11.1%† • Testing margin = 4.1% (37% relative to the expected rate) • Performance goal (PG) = 15.2% (expected rate of 11.1% plus testing margin of 4.1%) • Test significance level (α) = 0.025 (1-sided) • Power = 87.5% • Number of evaluable subjects = 675 • Expected rate of attrition = 3% • Total enrolment (evaluable Main Cohort) = 696 subjects † Estimated pooled rate from the fixed/random effects model based on the ITT TAVR arm data from PARTNER II S3i[e] and SURTAVI[f] e: Thourani VH, et al. *Lancet* 2016;387:2218-25 f: Reardon MJ, et al. N Engl J Med 2017:376:1321-31	
			Section 2 Success Criteria for the Primary Endpoint	If the *P* value from the one-sample z-test is <0.025, it will be concluded that the primary endpoint with the LOTUS Edge Valve System is less than the PG. This corresponds to the one-sided upper 97.5% confidence bound of the observed composite rate of all-cause mortality and all stroke in the Main Cohort at 1 year being < 15.2%.	
			Section 2, Statistical Test Method Primary Endpoint–Superiority	—	Updated study design; there is no statistical test for superiority for

Table 26.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
			Section 2, Sample Size Parameters Primary Endpoint – Superiority	—	the primary endpoint and there is no secondary endpoint
			Section 2, Success Criteria Primary Endpoint–Superiority	—	
			Section 2, Secondary Endpoint Statistical Hypothesis	—	
			Section 2, Statistical Test Method Secondary Endpoint	—	
			Section 2, Sample Size Parameters Secondary Endpoint	—	
			Section 2, Success Criteria Secondary Endpoint	—	
			Section 2 Bicuspid Nested Registry	The planned enrollment for the Bicuspid Nested Registry cohort is up to 100 subjects. Descriptive statistics for all endpoints will be summarized using both the ITT and implanted analysis sets.	Updated study design and for clarity
			Section 4 Introduction	The LOTUS Edge Valve System is introduced into the body using either the ~~investigational~~ iSleeve™ Introducer Set or the large Lotus Introducer Set. Both sets … Study subjects will be entered into the Roll-In Cohort, single-arm Main Cohort, or…	
			Section 4.1.1 Treatments…	The incidence of aortic stenosis… Many patients with severe and symptomatic aortic stenosis are successfully treated with surgical aortic valve replacement (SAVR), which can reduce symptoms… Propensity score analyses have suggested comparable mortality after TAVR or SAVR in some intermediate-risk patients… and 2 recent randomized, controlled trials (RCT) showed similar outcomes between	Additional literature references

Table 26.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				the two treatment groups… Meta-analyses have also shown similar long-term survival after TAVR compared to SAVR… Currently, TAVR is approved for use in AS patients considered inoperable or at intermediate to high surgical risk and expert consensus documents have outlined TAVR patient selection criteria... Added data from the following studies to **Table 4.1-1**: SURTAVI, REPRISE III, CoreValve Extreme Risk Study, EVOLUT R US Study, PORTICO Pre-CE Mark Study …Placement in a heavily calcified native valve can produce an incomplete seal between the bioprosthetic valve and aortic annulus, resulting in PVR, which in turn has been associated with increased mortality in some studies... The impact of mild PVR is less clear… recent meta-analysis suggested that mild PVR may also be associated with increased all-cause and cardiovascular mortality... The Lotus™ Valve System was… REPRISE IV will evaluate safety…	
			Section 4.1.2 REPRISE Clinical Program	Described below are results from studies that have reached their primary endpoints… Added REPRISE III results to Table 4.1-1	Added REPRISE III results to Table 4.1-1
			Section 4.1.2.1 REPRISE I Study	… 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 for device success~~ a mean gradient of 22 mmHg. Ten (10)… Table 4.1-2 shows clinical and echocardiographic outcomes to the end of the study (5 years). Valve function was excellent with minimal PVR and low clinical event rates. The results of the REPRISE I feasibility study support the safety and performance of the Lotus Valve System. Added new **Table 4.1-2: Outcomes to 5 Years in REPRISE I**	Data updated from 3 years to 5 years
			Section 4.1.2.2 REPRISE II Study	… Table 4.1-4 shows 30-day, 1-year, 2-year, 3-year, 4-year, and 5-year clinical and echocardiographic outcomes. Mortality at 30 days, 1 year, and 5 years was 4.2%, 11.0%, and 42.6%, respectively; the disabling stroke rate was 1.7%, 3.5%, and 7.0%. Mean aortic valve pressure gradient remained low at 12.58±5.66 mmHg (1 year) and	Data updated to 5 years in the Main Cohort and 4 years in the Full Cohort

Table 26.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				14.43±6.44 mmHg (5 years). There were no repeat procedures for valve-related dysfunction through 5 years. Core lab assessment of PVR at 30 days indicated no severe regurgitation and 1 case of moderate regurgitation; in 83.3% (80/96) of subjects there was trace/trivial or no PVR. The low PVR rate observed at 30 days was maintained at 1 year (89% with none/trivial PVR) and out to 5 years (80% with none/trivial PVR). The observed… **Table 4.1-4: Clinical and Echocardiographic Outcomes to 5 Years – REPRISE II Main Cohort (N=120)** updated with data at 3 years, 4 years and 5 years Table 4.1-5 shows device performance endpoints, clinical outcomes, and echocardiographic outcomes through 4 years for the full… …independent predictor of both. A recent meta-analysis suggested that mild PVR may also be associated with increased all-cause and cardiovascular mortality. The low PVR rate observed at 30 days with Lotus was maintained at 1 year and 4 years as most subjects (91% and 88%, respectively) had none/trace/trivial PVR, 2 subjects had moderate PVR at 4 years, and there was no severe PVR. **Table 4.1-5: Clinical and Echocardiographic Outcomes to 4 Years – REPRISE II Full Cohort (N=250)** updated with data at 2 years, 3 years, and 4 years.	
			Section 4.1.2.3 RESPOND Post-Market Surveillance Study	… Data through 30-day and 1-year follow-up are provided below… Table 4.1-7 shows secondary safety endpoint outcomes assessed at 30 days and 1 year in the RESPOND as-treated analysis set. At 30 days, all-cause mortality was 2.2%, in-hospital mortality was 1.8%, and disabling stroke was 2.3%. Mortality was 11.7% and disabling stroke was 4.0% at 1 year. Table 4.1-8 shows core laboratory TTE assessments pre-discharge and at 1 year in the as-treated analysis set. Mean aortic gradient improved significantly (P<0.0001) from 38.0±15.5 mmHg at baseline to 10.8±4.6 mmHg at discharge and remained low at 1 year (10.8±5.1 mmHg, P<0.0001). There was also a significant (P<0.0001) improvement in mean effective orifice area (EOA) from 0.7±0.2 cm^2 at baseline to 1.8±0.5 cm^2 at discharge, which was sustained at 1 year (1.8±0.4 cm^2, P<0.0001). There were no cases of severe PVR at discharge or 1 year. There were 3 cases of moderate PVR at discharge	Data updated from 30 days to 1 year, add RESPOND Extension

Table 26.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				and 2 cases (0.4%) at 1 year; in >90% of evaluable subjects PVR was trivial or absent. **Table 4.1-7: RESPOND Secondary Endpoints – VARC Safety Assessments at 30 Days and 1 Year Post-Procedure; As-Treated Analysis Set** updated with data at 1 year **Table 4.1-8: Core Laboratory Echocardiographic Assessments at Pre-Discharge and 1 Year, RESPOND As Treated Analysis Set** updated with data at 1 year After enrollment of the main RESPOND cohort was completed the study was extended to enroll an additional cohort (RESPOND Extension) to assess center-driven implantation technique with the commercially available Lotus Valve System with Depthguard™ technology. Depthguard results in a slightly decreased rate of retraction of the outer sheath during valve deployment. This minimizes interaction between the frame and the LVOT during deployment and could limit the need for PPM implantation. Table 4.1-10 shows clinical outcomes at 30 days and echocardiographic outcomes at pre-discharge. Mortality and disabling stroke were 0.0% and 2.0%, respectively, and new PPM implantation was 18.0%. There were no cases of moderate or severe PVR; in 86% of cases PVR was trivial or absent. Added **Table 4.1-10: RESPOND Extension – VARC Safety Assessments (30 Days) and Core Lab Echocardiographic Assessments (Pre-Discharge); As-Treated Analysis Set** In summary, the observed 30-day and 1-year outcomes among RESPOND subjects and 30-day outcomes in RESPOND Extension show good hemodynamic results, a very low PVR rate, low mortality, and overall favorable event rates. There also were no significant differences in pre-discharge echocardiographic or 30-day clinical outcome measures between subjects with and without a native bicuspid valve. The results from this study have demonstrated that the commercially available Lotus Valve System is a safe and effective	

Table 26.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				treatment for subjects with severe calcific aortic stenosis in routine clinical practice.	
			4.1.2.4 REPRISE III Randomized Controlled Trial	The REPRISE III pivotal study (REpositionable Percutaneous Replacement of Stenotic Aortic Valve through Implantation of Lotus™ Valve System – Randomized Clinical Evaluation; NCT02202434) includes a prospective, multicenter, randomized, controlled trial (RCT) designed to evaluate the safety and effectiveness of the Lotus™ Valve System (23mm, 25mm, or 27mm valve; test device) compared to a commercially available self-expanding transcatheter heart valve (CoreValve® device, Medtronic Corp, Dublin, Ireland; 26mm, 29mm, and 31mm valve; control device) in symptomatic subjects with severe calcific aortic stenosis who are considered extreme or high risk for surgical valve replacement. There were 912 subjects randomized at 55 centers in the United States, Germany, France, Australia, The Netherlands, and Canada. Subjects were considered enrolled in the study upon randomization. Clinical follow-up will extend through 5 years. The trial included independent core laboratory analysis and independent event adjudication with data validated by independent statisticians. The 30-day primary safety composite endpoint for REPRISE III includes all-cause mortality, stroke, life-threatening and major bleeding events, stage 2 or 3 acute kidney injury, and major vascular complications. The primary effectiveness endpoint for noninferiority includes the combined rate of mortality, disabling stroke, and moderate/severe PVR at 1 year post implant procedure. Other measurements incorporated the minimum data collection and endpoints recommended and defined by the VARC guidelines. Subject screening, data collection, and event assessments were as described for REPRISE II (Section 4.1.2.2). Data for the primary endpoint in the RCT have been published44. A total of 607 subjects were randomized to the Lotus group and 305 were randomized to the CoreValve group (ITT analysis set). Subject analysis groups are shown in Figure 4.1 1. The first-generation Lotus Valve System was used throughout the study while the second-generation CoreValve Evolut R device was introduced mid-way in the study. Thus, in the implanted analysis set of the CoreValve treatment	Addition of new study data

Table 26.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				group 51.5% of subjects received CoreValve and 48.5% received CoreValve Evolut R (153/297 and 144/297, respectively). Added new **Figure 4.1-1: REPRISE III Randomized Subject Analysis Groups** The REPRISE III primary safety endpoint was met because in the implanted analysis set the rate for the Lotus group (20.3%) was non-inferior to the rate for the CoreValve group (17.2%). Non-inferiority was concluded because the one-sided upper 97.5% confidence bound on the difference between treatment groups (Lotus minus CoreValve; 3.1%) was less than the non-inferiority margin of 10.5% with a P value <0.025 (*P*=0.0027). Non-inferiority was also shown for the ITT and as-treated analysis sets. The primary effectiveness endpoint was met because in the implanted analysis set the rate for Lotus group (15.4%) was non-inferior to the rate for CoreValve (25.5%). Non-inferiority was concluded because the one-sided upper 97.5% confidence bound on the difference between treatment groups (Lotus minus CoreValve; -4.41%) was less than the non-inferiority margin of 9.5% with a *P* value <0.025 (*P* <0.0001). Non-inferiority was also shown for the ITT and as-treated analysis sets. The rate of the primary effectiveness endpoint for Lotus was shown to be superior to that for CoreValve in the ITT analysis set (*P*=0.0006) and also in the implanted and as-treated analysis sets. Table 4.1 11 shows clinical and echocardiographic outcomes at 30 days and 1 year. The following were similar between the 2 cohorts: • All-cause mortality in the CoreValve arm and Lotus arm was 2.3% and 2.5%, respectively (*P* =0.86), at 30 days and 13.5% and 11.9%, respectively (*P*=0.51), at 1 year. • Cardiovascular mortality was 2.3% (CoreValve) and 2.3% (Lotus, *P*=0.99) at 30 days and 9.8% (CoreValve) and 7.7% (Lotus, *P*=0.29) at 1 year. • The overall stroke rate in the CoreValve and Lotus cohorts was 4.3% and 4.8%, respectively (*P*=0.72), at 30 days and 9.4% and 7.0%, respectively (*P*=0.20), at 1 year.	

Table 26.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				• The rate of major vascular complications was 5.3% (CoreValve) and 7.0% (Lotus, *P*=0.32) at 30 days and 6.1% (CoreValve) and 7.7% (Lotus, *P*=0.38) at 1 year. • Life-threatening/disabling bleeding was 5.0% (CoreValve) and 8.0% (Lotus, *P*=0.09) at 30 days and 9.8% (CoreValve) and 9.9% (Lotus, *P*=0.96) at 1 year. The following were statistically significantly different between the 2 cohorts: • The disabling stroke rate in the CoreValve and Lotus cohorts was 3.3% and 2.0%, respectively (*P*=0.23), at 30 days and 7.1% and 3.6%, respectively (*P*=0.02), at 1 year. • The rate of permanent pacemaker implantation among subjects without a prior pacemaker was 19.6% (CoreValve) and 35.5% (Lotus, *P* <0.001) at 30 days and 23.0% (CoreValve) and 41.4% (Lotus, *P* <0.001) at 1 year. • The valve thrombosis rate was 0.0% for both cohorts at 30 days; it was 0.0% (CoreValve) and 1.5% (Lotus, P=0.03) at 1 year. • Repeat procedures for prosthetic valve-related dysfunction occurred in 1.0% of CoreValve subjects and 0.0% of Lotus subjects at 30 days (*P*=0.04) and 2.0% (CoreValve) and 0.2% (Lotus) by1 year (*P*=0.007). • Prosthetic valve malpositioning (including valve migration, valve embolization, and ectopic valve deployment to discharge/7 days) occurred in 2.6% of subjects in the CoreValve group and 0.0% of subjects in the Lotus group (*P*<0.001). • TAV-in-TAV deployment occurred in 3.0% of subjects in the CoreValve group and in no subjects in the Lotus group (*P*<0.001). • Mean gradient was significantly lower and EOA was significantly higher in the CoreValve group at discharge and beyond (both *P* <0.001). • There was significantly less PVR with Lotus compared to CoreValve at all time points (*P*<0.001). Added new **Table 4.1-11: Clinical and Echocardiographic Outcomes at 30 Days and 1 Year in REPRISE III RCT** In conclusion, in this large (N=912) randomized comparison of two different types of TAVR platforms, the Lotus Valve System was non-	

Table 26.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				inferior to the commercially available CoreValve for the composite primary safety endpoint at 30 days. Lotus showed superiority for the composite primary effectiveness endpoint at 1 year, driven by significantly fewer disabling strokes (3.6% vs 7.1%, *P*=0.02) and significantly less moderate or severe PVR (0.9% vs 6.9%, *P*<0.0001; core lab determination). The frequency of overall stroke at 1 year was 7.0% with Lotus and 9.4% with CoreValve; the repositionability of Lotus did not lead to a higher stroke rate compared to CoreValve. Recently reported 1-year stroke rates include 5.6% among high-risk subjects in the adjudicated SAPIEN 3 registry and 8.8% and 12.6% among TAVR and SAVR subjects, respectively, in the U.S. CoreValve High Risk Study. Lower stroke rates have been reported in lower-risk subject groups. Moderate or greater PVR has been associated with an increased risk of mortality. The impact of mild PVR is less clear although a recent meta-analysis suggested that mild PVR may also be associated with increased all-cause and cardiovascular mortality. Reported rates for moderate or greater PVR with newer generation devices have ranged from 1.5% with the balloon-expandable SAPIEN 3 valve to 5.3% with Evolut R with lower rates in intermediate compared to high risk subjects. There were more new pacemaker implantations (41.4% vs 23.0%, *P*<0.0001 among subjects without a prior pacemaker) at 1 year with Lotus. Pacemaker implantation is associated with subject morbidity and increased cost (including repeat hospitalization) but has not been associated with decreased survival in other studies of high risk subjects. A recently published meta-analysis found that subjects with and without PPM post TAVR had similar rates for all-cause mortality, cardiovascular mortality, MI, and stroke at 30 days and 1 year. This analysis did show that improvement in LVEF was significantly greater in subjects without PPM. Valve thrombosis was uncommon but there were significantly more cases, as defined by VARC criteria, with Lotus (1.5% vs. 0%, P=0.03). Most were identified based on increased mean aortic gradient at protocol-directed follow-up echocardiography and all showed a decrease in mean gradient after anticoagulation therapy. These results are consistent with a recent registry report based on CT showing subclinical leaflet thrombosis rates of 4% with surgical valves and 12%	

Table 26.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				with TAVR valves and suggesting that the supra-annular CoreValve may have a lower rate compared to TAVR valves with an annular location (CoreValve/Evolut R: 6%; Lotus: 14%; Edwards [Sapien, SAPIEN XT, and SAPIEN 3]: 14%; Portico: 30%). A recent single-center retrospective analysis (281 balloon-expandable, 305 self-expanding, 56 Lotus) found an overall incidence of 2.8% for clinical valve thrombosis. Reported rates were 4.6% for SAPIEN valves, 1.0% for CoreValve/Evolut R, and 3.6% for Lotus. At 1 year, valve malpositioning, repeat procedures, and TAV-in-TAV deployment were all less common with Lotus. The observed rate of TAV-in-TAV with CoreValve was 2.3%; rates of TAV-in-TAV with CoreValve in prior US pivotal CoreValve trials have ranged from 1.3% to 6.7%. Overall, outcomes in the REPRISE III RCT support the safety and efficacy of the Lotus Valve System.	
			4.1.2.5 REPRISE Japan	The objective of the REPRISE Japan clinical trial (REpositionable Percutaneous Replacement of Stenotic Aortic Valve through Implantation of Lotus™ Valve System – Clinical Evaluation in Japan; NCT02491255) was to confirm the safety and effectiveness of the Lotus™ Valve System in the Japanese medical environment for TAVR in symptomatic subjects with calcific, severe native aortic stenosis considered at high or extreme risk for SAVR. The 30-day primary safety composite endpoint includes all-cause mortality, stroke, life-threatening and major bleeding events, stage 2 or 3 acute kidney injury, and major vascular complications. The primary effectiveness endpoint is a composite at 6 months of all-cause mortality and disabling stroke and moderate or greater PVR based on core lab assessment. Other measurements incorporated the minimum data collection and endpoints recommended and defined by the VARC guidelines. Subject screening, data collection, and event assessments were as described for REPRISE II (Section 4.1.2.2). There were 40 evaluable subjects enrolled at 5 centers in the transfemoral arm of REPRISE Japan. The primary safety composite endpoint rate was 15.0% (6/40) at 30 days and the primary effectiveness composite endpoint was 5.3% (2/38) at 6 months. Table 4.1-12 shows clinical and echocardiographic outcomes at 30 days, 6 months, and 1 year. Mortality through 1 year was low (7.5%) as was disabling stroke	Addition of new study data

Table 26.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				(2.5%). There was no moderate or severe PVR. Overall, outcomes were similar to that seen with Lotus in REPRISE II (Section 4.1.2.2) and REPRISE III (Section 4.1.2.4) and demonstrated consistent safety and effectiveness results with the Lotus Valve System in Japanese subjects. Added new **Table 4.1-12: 30-Day, 6-Month, and 1-Year Outcomes – REPRISE Japan Evaluable Transfemoral Cohort (N=40)**	
			Section 4.1.2.6 REPRISE NGDS Study	… evaluating a modified version of the delivery system that was studied in REPRISE I, REPRISE II, REPRISE III, and RESPOND. …compatibility with the LOTUS Edge device. A third cohort (Cohort C) subsequently enrolled 21 subjects who were treated with a further refined version of the LOTUS Edge delivery system. In some Cohort C subjects a further refined version of the iSleeve Introducer was used. The primary endpoint in REPRISE NG DS… The primary endpoint was achieved in 10/10 subjects in Cohort A, 5/7 in Cohort B (in 1 subject a valve was not implanted and in 1 subject a valve was implanted using the current Lotus Valve System), and 21/21 in Cohort C. Table 4.1-13 shows core lab analyses of prosthetic valve performance as assessed by TTE at discharge/7 days post procedure (secondary endpoint) and valve function at 30 days and 1 year for the 3 cohorts. In all cohorts, mean aortic valve area and mean gradient improved at discharge and remained improved at 30 days and 1 year. There were no cases of moderate or severe PVR at discharge, 30 days, or 1 year in any cohort; the majority of patients had no PVR or trace PVR at all time points. Table 4.1-14 shows rates of CEC-adjudicated VARC-defined events through discharge/7 days, 30 days, 6 months, and 1 year. In Cohort A, one subject experienced the majority of events and subsequently died on day 13 post implant. In Cohort B, events were minimal. In Cohort C, new permanent pacemakers were placed in 2 subjects by 1 year for a rate of 9.5% (2/21) among all subjects and 11.1% (2/18) among subjects without a prior pacemaker. In summary, outcomes to 1 year in the REPRISE NG DS study demonstrate acceptable performance and safety of the Lotus Valve with the next generation delivery system.	Update previous data and add new study data

Table 26.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				Updated **Table 4.1-13: Valve Performance by TTE, Core Lab Analysis – REPRISE NG DS Cohorts A, B and C** with data at 1 year and Cohort C data Updated **Table-4.1-14: Discharge, 30-Day, 6-Month, and 1-Year Clinical Outcomes in REPRISE NG DS Cohorts A, B and C** with data at 6 months and 1 year and Cohort C data	
			4. 1.2.7 REPRISE EDGE	The prospective, single-arm REpositionable Percutaneous Replacement of NatIve StEnotic Aortic Valve through Implantation of LOTUS EDGE Valve System – Evaluation of Performance and Safety study (REPRISE EDGE; NCT02854319; N=15) has the same overall study design as REPRISE NG DS (Section 4.1.2.5) and assessed acute performance and safety of the same LOTUS Edge design that was used in Cohort C. The primary endpoint was the mean aortic valve pressure gradient at discharge as measured by echocardiography and assessed by an independent core laboratory. Secondary endpoints included technical success and device performance peri- and post-procedure based in part on VARC criteria. At discharge, the mean aortic gradient was 14.4±4.1 mmHg (N=15). Technical success was 100% and all attempts at repositioning or retrieving the valve were successful, and there was no moderate or severe PVR at discharge. Table 4.1 15 shows clinical and echocardiographic outcomes at 30 days and 1 year. There was no mortality and 1 disabling stroke through 1 year; PPM were placed in 2 subjects by 30 days for a rate of 13.3% among subjects without a prior PPM. Mean aortic valve area and mean gradient were improved at 30 days and 1 year with no moderate or severe PVR. Overall, outcomes with LOTUS Edge are consistent with outcomes observed in REPRISE II/II Extension and REPRISE III and with other TAVR studies using the VARC metrics. Added **Table 4.1-15: 30-Day, and 1-Year Outcomes – REPRISE EDGE (N=15)**	Addition of new study data
			Section 4.2 Justification for the Study	Because the investigational device, the LOTUS Edge Valve System, consists of essentially the same pre-loaded, stent-mounted tissue valve prosthesis as the Lotus Valve System evaluated in the REPRISE I, REPRISE II, REPRISE III, REPRISE Japan, and RESPOND studies but	Updated to mention additional REPRISE studies and for clarity

Table 26.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				with a catheter delivery system designed for improved deliverability (evaluated in the REPRISE NG DS and REPRISE EDGE studies) the anticipated benefits and risks are very similar. … Like the Lotus Introducer, the ~~investigational~~ iSleeve Introducer Set…	
			Section 5	**Investigational Device Description** The investigational LOTUS Edge™ Valve System is intended to improve aortic valve function for symptomatic subjects with severe aortic stenosis who are at intermediate risk for standard surgical aortic valve replacement (SAVR), including those who have a bicuspid native valve.	Change in study design to a single-arm study (no control device)
			Section 5.1	**LOTUS Edge Valve System** **Figure 5.1-1: Overview of Principal Components of the LOTUS Edge Valve System** – updated with a newer picture **Figure 5.1-2: LOTUS Edge Valve Implant** – updated with a newer picture The controller assembly is shown in Figure 5.1-3 (locked configuration in the top image) ~~and Figure 5.1-4 (controller door pulled forward)~~. **Figure 5.1 3: LOTUS Edge Controller** Top: Locked configuration. Bottom: Door pulled forward allowing the valve to be released The large Lotus Introducer Set or, when available, the iSleeve Introducer Set (Figure 5.1-4) will be used as an accessory to the LOTUS Edge Valve System during the procedure. In countries where the introducer sets are approved, the commercial devices will be used. In countries where they are not approved, they will be considered investigational devices. They both include a dilator and an introducer sheath with a hydrophilic coating that, when activated, increases the lubricity of the surface to aid in delivery. ~~The small Lotus Introducer…~~ The large Lotus Introducer is intended for use with the 23mm, 25mm, or 27mm LOTUS Edge valve in subjects with femoral vascular access ≥6.5 mm. The sheath component of the iSleeve is expandable, which allows for transient sheath expansion during delivery system introduction. Temporary	Updated device pictures; slight change in description of iSleeve; removal of the small Lotus Introducer set

Table 26.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				expansion of the access vessel reduces the time the access vessel is expanded during device introduction and therefore potentially reduces vessel trauma. ~~The 14F iSleeve Introducer Set…~~ The 15F iSleeve is capable of introducing the 23mm, 25mm and 27mm LOTUS Edge valve sizes into subjects with femoral vascular access ≥5.9 mm.	
			5.2 Edwards SAPIEN 3… (Control)	~~The control device is…~~ **(section removed)**	Study design change to single-arm version
			5.3 Device Labeling	**5.2 Device Labeling** The study Manual of Operations includes the IFUs for the LOTUS Edge Valve System and, when available, the iSleeve… The IFU for the large Lotus Introducer Set will also be provided in the study Manual of Operations. The label will also include the above, with the exception of the investigational device statement for countries where the device is commercially available… ~~**5.3.2 Control Device Information…**~~	Updated for clarity; removed reference to control device because this is now a single-arm study
			7. Study Endpoints	Outcomes will be assessed on an intention-to-treat (ITT) basis and an implanted basis ~~and an as-treated basis~~. The ITT analysis population includes all subjects who sign the Informed Consent Form (ICF; see Section 21) and are enrolled in the trial (see Section 10.1 for point of enrollment) ~~and are randomized~~ regardless of whether a study device valve is implanted. The implanted analysis population includes ITT subjects who are implanted with the study valve. ~~The as-treated population…~~ Endpoint definitions can be found in Table 26.2-1.	Text updated for clarity with updated study design
			Section 7.1 Primary Endpoint	The primary endpoint is a composite of all-cause mortality and all stroke ~~and mild or greater paravalvular aortic regurgitation (PVR; based on core lab assessment)~~ at 1 year…	Updated for the single arm design
			Section 7.2 Secondary Endpoint	— **(section removed)**	
			Section 7.3 Additional Measurements	**7.2 Additional Measurements** Additional measurements… will be collected peri- and post-procedure, at discharge or 7 days post-procedure (whichever comes first), 30 days, ~~6 months,~~ and 1, 2, 3, 4, and 5 years post index procedure… -Neurological status (see **Note 5** below) as determined by the following:	Text updated for clarity and addition of CT Imaging Substudy

Table 26.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				~~o Neurological physical exam…~~ o National Institutes of Health Stroke Scale (NIHSS; performed by a neurology professional or certified personnel) at discharge and 1 year o and modified Rankin Scale (mRS) assessments, which must be performed at baseline and pre-specified timepoints for all enrolled subjects. NIHSS and mRS must be performed by a neurology professional or certified personnel. o For subjects diagnosed with a stroke, a neurological physical exam, mRS, and NIHSS must be performed after the event; mRS must also be administered at 90±14 days following a stroke; the simplified mRS questionnaire may be used for this follow-up assessment. The neurological physical exam must be conducted by a neurologist, neurology fellow, neurology physician assistant, or neurology nurse practitioner… - For subjects in the Bicuspid Nested Registry, a CT scan at 30 days post LOTUS Edge Valve implantation. The data will be evaluated by an independent CT core laboratory - For subjects in the CT Imaging Substudy, a 4D CT scan at 30 days and at 1 year post LOTUS Edge valve implantation to assess the prevalence of reduced leaflet mobility and its relationship, if any, to clinical events. The data will be evaluated by an independent CT core laboratory. **Note 5**: For subjects diagnosed with a stroke, a neurological physical exam, mRS, and NIHSS must be performed after the event; mRS must also be administered at 90±14 days following a stroke; the simplified mRS questionnaire may be used for this follow-up assessment. **7.3 Overview of Objectives and Endpoints** Table 7.3-1 provides an overview of the aforementioned study objectives and endpoints and a justification for the specific endpoints. **Table 7.3-1: Overview of Objectives and Endpoints** – added table	
			Section 8.1 Scale and Duration	The REPRISE IV clinical study includes a prospective, multicenter, single-arm trial (Main Cohort; N=696) designed to evaluate the safety and effectiveness of the LOTUS Edge Valve System when used with the	Updated for clarity, including the single arm design and for addition

Table 26.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				Lotus™ Introducer Set or, when available, the iSleeve™ Introducer Set for TAVR in symptomatic subjects who have severe aortic stenosis and who are at intermediate risk for SAVR. There will be a roll-in phase (up to 100 subjects) for centers that do not have previous experience implanting the LOTUS Edge Valve. There will also be a single-arm nested registry cohort of subjects who have a bicuspid native valve to assess safety and effectiveness (Bicuspid Nested Registry; N=100). Selected centers with the ability to perform high quality 4D computed tomography (CT) scans will include up to 200 subjects from the Main Cohort in a CT Imaging Substudy to assess the prevalence of reduced leaflet mobility and its relationship, if any, to clinical events. All subjects in these centers will be approached for consent to participate in the CT study. If 200 subjects have not enrolled in the CT Imaging Substudy by completion of enrollment in the main cohort, additional subjects who meet the REPRISE IV eligibility criteria will be enrolled in a separate CT Imaging Cohort to achieve a total of 200 subjects in the CT Imaging Substudy Figure 8.1 1 shows the study design. Inserted new **Figure 8.1-1: REPRISE IV Study Design** All subjects implanted will be followed at baseline, peri- and post-procedure, at discharge or 7 days post-procedure (whichever comes first), 30 days, ~~6 months,~~ and then annually for up to 5 years post-procedure. Enrolled subjects who do not have a study device implanted will be assessed through 1 year post procedure for safety/adverse events. The REPRISE IV study will be conducted in accordance with 21 CFR Parts 11, 50, and 54; the relevant parts of the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practices (GCP); the International Standard ISO 14155 Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice; ethical principles that have their origins in the Declaration of Helsinki; and pertinent individual country/state/local laws and regulations. The study shall not begin until the required approval/favorable opinion from the Institutional Review Board/Human Research Ethics Committee (IRB/HREC) and/or regulatory authority has been obtained, if appropriate. See Section 11 below for additional information on study design and data collection.	of the CT Imaging Substudy

Table 26.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				The REPRISE IV study is registered at ClinicalTrials.gov (identifier NCT03618095).	
			Section 8.2 Treatment Assignment	Screening materials…enrollment. All subjects will have unique identification numbers. **Note 1**: Subjects who have a bicuspid native valve will be enrolled in a separate nested registry cohort to assess safety and effectiveness. There will be a roll-in phase for centers that do not have previous experience implanting the LOTUS Edge Valve; each of these centers will perform at least 2 roll-in cases before commencing enrollment in the Main Cohort and Bicuspid Nested Registry cohort.	
			Section 8.2.1 Treatment	See Section 5 for a detailed description of the test device and information on device sizes. … The large Lotus Introducer Set or, when available, the iSleeve Introducer Set is used as an accessory in the procedure. In countries where the introducer sets are approved, the commercial devices will be used. In countries where they are not approved, they will be considered investigational devices.	Updated for clarity regarding the test valve and introducer.
			Section 8.3 Study Design Justification	There will be up to 895 subjects in REPRISE IV. In…, up to 100 subjects will be enrolled in the roll-in…, 695 subjects will be enrolled in the Main Cohort, and 100 subjects will be enrolled in the Bicuspid Nested Registry cohort. Up to 50 centers in the United States and Australia will participate... Per… antiplatelet therapy with aspirin and a P2Y12 inhibitor is recommended after TAVR…	Updated for the study design and for clarity
			Section 9.1 Study Population and Eligibility	The study will include subjects presenting with symptomatic severe aortic stenosis who are considered at intermediate risk for surgical valve replacement. Because aortic stenosis most commonly occurs in the very elderly, women are well represented in TAVR trials. Traditionally underrepresented populations (elderly and women) are expected to be included in the subject population as allowed by governing law/national regulation; as the very elderly will represent the majority of subjects enrolled in the trial, efforts to maximize retention are by definition targeted to traditionally under-represented groups. The inclusion and exclusion criteria are not expected to have a negative effect on recruitment or retention of said populations. In the United States, the subjects eligible for inclusion in this study are likely to be Medicare	Updated for clarity

Table 26.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				patients due to their expected age and the results of this study are likely to be highly generalizable to a Medicare population. All efforts will be made to minimize attrition in REPRISE IV. Prior…	
			Section 9.2 Inclusion Criteria	**Table 9.2-1: REPRISE IV Inclusion Criteria** IC2. A subject in the Bicuspid Aortic Valve Nested Registry cohort must have documented bicuspid aortic valve morphology based on CT assessment and confirmed by the CT core lab with hemodynamic parameters that meet the criteria in IC1. IC3. Subject has a documented aortic annulus size of ≥20 mm and ≤27 mm based on the center's assessment of pre-procedure diagnostic imaging (and confirmed by the CRC) ~~and, for the randomized cohort, is deemed treatable with an available size of both test and control device.~~ IC5. Heart team (which must include an experienced cardiac interventionalist and an experienced cardiac surgeon) agrees that the subject is at intermediate risk of operative mortality (≥3% and <8% at 30 days) and TAVR is appropriate… IC6. Heart team ~~(which must include a cardiac interventionalist and an experienced cardiac surgeon)~~ agrees that the subject is likely to benefit from valve replacement. ~~IC7. Heart team agrees (a priori) on treatment strategy for concomitant coronary artery disease (if present). The strategy must be the same regardless of whether the patient is to be treated with a test or control device.~~ IC7. Subject (or legal representative) has been informed of the study requirements and the treatment procedures and provides written informed consent. IC8. Subject, family member, and/or legal representative agree(s) and subject is capable of returning to the study hospital for all required scheduled follow up visits. IC9. Subject is expected to be able to take the protocol-required adjunctive pharmacologic therapy.	
			Section 9.3 Exclusion Criteria	EC1. Subject has a unicuspid or bicuspid aortic valve (not applicable to subjects in the Bicuspid Nested Registry cohort).	

Table 26.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				Note: Subjects in the Bicuspid Nested Registry cohort will have a documented Sievers Type 0~~2~~ or Sievers Type 1 bicuspid valve based on CT assessment and confirmed by the CT core lab. Subjects are not eligible for inclusion in the Bicuspid Nested Registry cohort if the maximum diameter of the ascending aorta is >45 mm or if the subject has another indication for aortic root replacement. Subjects with a Sievers Type 2 bicuspid valve are not eligible for enrollment in any study cohort. EC4. Subject is on renal replacement therapy or has or has GFR <20 ~~(based on Cockcroft-Gault formula)~~. EC5. Subject has a pre-existing prosthetic aortic or mitral valve. EC6. Subject has severe (4+) aortic, tricuspid, or mitral regurgitation. EC7.Subject has moderate to severe mitral stenosis (mitral valve area ≤1.5 cm^2 and diastolic pressure half-time ≥150 ms, Stage C or D). EC8. Subject has a need for emergency surgery for any reason. EC9. Subject has a history of endocarditis within 6 months of index procedure or evidence of an active systemic infection or sepsis. EC10. Subject has echocardiographic evidence of new intra-cardiac vegetation or intraventricular or paravalvular thrombus requiring intervention. ~~EC11. Subject requires chronic anticoagulation therapy after the implant procedure and cannot be treated with warfarin or other vitamin K antagonist (other anticoagulants are not permitted in the first month) for at least 1 month concomitant with either aspirin or clopidogrel*.~~ EC11.Subject has platelet count <50,000 cells/mm^3 or >700,000 cells/mm3, or white blood cell count <1,000 cells/mm^3. EC12. Subject has had a gastrointestinal bleed… EC16. Subject has any therapeutic invasive cardiac or vascular procedure ~~resulting in a permanent implant that is performed~~ within 30 days prior to the index procedure (~~unless part of planned strategy for treatment of concomitant coronary artery disease~~ except for balloon aortic valvuloplasty or pacemaker or implantable cardioverter defibrillator implantation, which are allowed). EC20. Subject has arterial access that is not acceptable for the study device delivery system as defined in the device Instructions For Use.	

Table 26.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				EC22. Subject has current problems with substance abuse (e.g., alcohol, etc.) that may interfere with the subject's participation in this study. Additional exclusion criteria apply to subjects considered for enrollment in the CT Imaging Substudy as listed below: AEC1. Subject has eGFR <30 mL/min (chronic kidney disease stage IV or stage V). AEC2. Subject has atrial fibrillation that cannot be rate controlled to ventricular response rate < 60 bpm. AEC3. Subject is expected to undergo chronic anticoagulation therapy after the index procedure. **Note**: Subjects treated with short-term anticoagulation post procedure can be included in the imaging substudy; in these subjects the 30-day imaging will be performed 30 days after discontinuation of anticoagulation.	
			10.1 Point of Enrollment	Subjects who are confirmed eligible for the study by the CRC (see Section 22.2) and who provided written informed consent are considered enrolled in the study as soon as an attempt is made to insert the LOTUS Edge Valve System into the subject's femoral artery.	Updated per the new study design
			10.2 Withdrawal	All subjects enrolled in the clinical study (including those withdrawn from the clinical study or lost to follow-up) shall be accounted for and documented. If a subject withdraws from the clinical investigation, the reason(s) shall be reported. Reasons for withdrawal include but are not limited to physician discretion, subject choice to withdraw consent, or death. If such withdrawal is due to problems related to investigational device safety or performance, the investigator shall ask for the subject's permission to follow his/her status/condition outside of the clinical study. While all efforts will be made to minimize attrition, subjects may withdraw from the study at any time, with or without reason and without prejudice to further treatment. Withdrawn subjects will not undergo any additional study follow-up, nor will they be replaced. The 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	Updated for clarity

Table 26.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				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, unless local regulations apply. No new data will be collected after withdrawal. All applicable case report forms up to the point of subject withdrawal and an "End of Study" form for the subject must be completed. If the withdrawal is due to investigator discretion, the investigator should follow-up with the subject per standard of care. Information on determining if a subject is lost to follow-up can be found in Section 11.10.6.	
			10.3. End of Study Definition	This clinical trial will be considered completed when subjects are no longer being examined or the last subject's last study visit as outlined in the data collection schedule (Table 11.1 1) has occurred. All subjects who receive a test device will be evaluated at discharge or 7 days (whichever comes first), 30 days, 1 year, 2 years, 3 years, 4 years, and 5 years post index procedure. All visits are office visits. A subject's participation in the study will be considered complete after the 5-year visit. For subjects who do not receive a test device, participation in the study will be considered complete after the 1-year visit.	
			11.1 Data Collection	Updated figure and table: **Figure 11.1-1: REPRISE IV Data Collection Scheme** **Table 11.1-1: Study Event Schedule** c: Study-specific consent… as necessary. **Note 2:** The subject should undergo the index procedure within 30 days after signing the study Informed Consent Form. d: ~~Neurological physical examination must be performed by a neurologist, neurology fellow, neurology physician assistant, or neurology nurse practitioner who is independent of the study.~~ NIHSS and mRS must be performed by a neurology professional or certified personnel (external certification for NIHSS; internal or external certification for mRS). The NIHSS and mRS assessors should be independent (not involved with the care of study subjects). For subjects diagnosed with a stroke, a neurological physical exam, mRS, and	

Table 26.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				NIHSS must be performed after the event; mRS must also be administered at 90±14 days after a stroke; the simplified mRS questionnaire may be used for this follow-up assessment. The neurological physical examination must be performed by a neurologist, neurology fellow, neurology physician assistant, or neurology nurse practitioner who is independent of the study. If a subject who has not received a study device ~~(investigational or control)~~ experiences a stroke within the first 1 year after the index procedure, mRS must be performed on that subject after the event; mRS must also be administered at 90±14 days after a stroke and the results must be reported to the Sponsor h: Frailty, disability, and comorbidity risk assessments must be captured at screening: height, weight, ~~cognitive function (Mini-Cognitive Assessment for Dementia),~~ strength… m: For subjects in the Bicuspid Nested Registry cohort, a computed tomography scan at 30 days post LOTUS Edge Valve implantation. Please refer to the CT Core Laboratory procedure guidelines (see study Manual of Operations). Results must be sent to the CT Core Laboratory. q: Procedural cine-angiogram including the baseline images of the aortic complex and the final post-deployment aortogram of the ascending aorta must be performed and sent to the CT/X-Ray Core Laboratory for analysis. ~~Rotational angiography of the valve frame is required with results sent to the Core Laboratory.~~ t: For subjects in the CT Imaging Substudy, a 4D CT scan at 30 days and at 1 year post LOTUS Edge valve implantation must be done. Please refer to the CT Core Laboratory procedure guidelines (see study Manual of Operations). The data must be sent to the independent CT core laboratory.	
			Section 11.2 Study Candidate Screening	Subjects will be evaluated for eligibility by the center heart team (which must include an experienced cardiac interventionalist and an experienced cardiac surgeon). The heart team should take into account the Society of Thoracic Surgeons (STS) score as well as other clinical comorbidities not accounted for in the risk calculation. Eligible subjects will have agreement from the heart team that the subject is at intermediate	

Table 26.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				operative risk of mortality with SAVR (see Table 9.2 1 for inclusion criteria~~; see definition of operative risk in Table 26.2 1~~). Risk…	
			Section 11.4 Screening Assessments	Results from the screening tests and procedures listed below ~~(including any planned concomitant treatment of CAD and any planned use of BAV during the index procedure)~~ must be submitted to the CRC …of subject eligibility. ~~For the randomized cohort, a subject should be randomized after CRC approval and within 7 calendar days of CRC approval.~~ **Note 1:** It is recommended that predilatation be performed unless there is minimal calcification of the annulus and leaflets. ~~To minimize bias, planned use of BAV during the index procedure should not be influenced by type of study valve and therefore should be determined and reviewed and approved by the CRC prior to subject randomization.~~ Subjects… **Note 2:** Additional concomitant procedures, including percutaneous coronary intervention, are not allowed during the index procedure. Centers will… • Clinical assessments… o Risk… reimbursement ~~o Planned treatment of CAD and lanned use of BAV (i.e., predilatation)~~ • Frailty… o Body Mass… ~~o Cognitive Function: Mini-Cognitive Assessment for Dementia[126,127] (see study Manual of Operations)~~ o Strength…	
			11.5 Baseline Assessments	The following assessments must be completed within 30 days… • Confirmation of CRC approval date ~~• Neurological physical examination, which must be performed by a neurologist, neurology fellow, neurology physician assistant, or neurology nurse practitioner (see Table 11.1 1).~~ • NIH Stroke Scale…	
			11.6 Pre-procedure Medications	…loading dose. $P2Y_{12}$ Inhibitor	

Table 26.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				A loading dose of a $P2Y_{12}$ inhibitor (clopidogrel at a dose of ≥300 mg is recommended; for other $P2Y_{12}$ inhibitors recommended doses are 60 mg for prasugrel and 180 mg for ticagrelor) is required for subjects who have not been on $P2Y_{12}$ inhibitor therapy for ≥72 hours at the time of the index procedure. The loading dose must be administered prior to the implant procedure. **Note:** If a subject is treated with anticoagulation, either a $P2Y_{12}$ inhibitor or aspirin is required prior to the implant procedure (but both aspirin and a $P2Y_{12}$ inhibitor are not required). ~~**Note 1:** An alternative $P2Y_{12}$ inhibitor (e.g., ticlopidine) may be prescribed if subject is allergic to or intolerant of clopidogrel.~~ ~~**Note 2:** If a subject requires chronic anticoagulation, either clopidogrel or aspirin is required prior to the implant procedure (but both aspirin and clopidogrel are not required). The subject should not receive a $P2Y_{12}$ inhibitor aside from clopidogrel.~~	
			11.7 Index Procedure	…technical aspects of the index procedure. **Note 1:** Additional concomitant procedures, including percutaneous coronary intervention, are not allowed during the index procedure. **Note 2:** The subject should undergo the index procedure within 30 days after signing the study Informed Consent Form. The preparation of the subject for the percutaneous procedure will be performed following standard techniques~~. It is recommended that predilatation be performed unless there is minimal calcification of the annulus and leaflets. To minimize bias, planned use of BAV during the index procedure should not be influenced by type of study valve and therefore should be determined before subject randomization. BAV must be performed in patients in the bicuspid registry.~~ Transfemoral access… The large Lotus Introducer Set or, when available, the iSleeve Introducer Set iSleeve/Lotus Introducer is prepared and introduced in the patient's femoral artery, as described in the iSleeve/Lotus Introducer IFU. A balloon valvuloplasty… heart rhythm must be assessed and documented (12-lead ECG is not required)…	Updated for the new study design and for clarity

Table 26.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				Note 3: It is recommended that predilatation be performed unless there is minimal calcification of the annulus and leaflets; BAV must be performed in subjects in the Bicuspid Nested Registry cohort. **Note 4:** If the subject becomes… **(11.7.1 Edwards SAPIEN 3 removed)** The LOTUS Edge Valve implantation procedure requires two operators: First and Second Operators. Both… 3) The catheter is… mechanically expanded and locked into the desired position… 5) If the position…using the ~~radiopaque marker~~ frame as a guide. The valve… • Device deficiencies assessment for the LOTUS Edge Valve System ~~and the iSleeve Introducer Set (if used)~~ **Note 5**: All LOTUS Edge Valve implantation procedures will be performed with the support/presence of trained BSC personnel (see Section 17.4.2). **Note 6**: In countries where the introducer sets are approved, a device deficiency should be reported as a complaint.	
			11.8 Post-Procedure	• Per society… Subjects must be treated with aspirin and a $P2Y_{12}$ inhibitor for at least 1 month… º After the valve implant procedure, treatment with a $P2Y_{12}$ inhibitor is required for at least 1 month. Dosing should follow local standard of care. º If a subject is treated with chronic anticoagulation, either a $P2Y_{12}$ inhibitor or aspirin is required after the implant procedure in addition to the anticoagulant therapy (but both aspirin and a $P2Y_{12}$ inhibitor are not required). The subject must be treated with an oral anticoagulant (OAC) and either a $P2Y_{12}$ inhibitor (clopidogrel recommended) or aspirin for at least 1 month. ~~After 1 month, subjects requiring chronic anticoagulation may be switched from warfarin or other vitamin K antagonist to a new oral anticoagulant (NOAC) at the discretion of the treating physician. The subject should not receive a $P2Y_{12}$ inhibitor in combination with a NOAC but may be treated with a NOAC plus aspirin…~~	Updated to reflect current therapy recommendations

Table 26.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				• Cardiac enzymes… twice within 6 to 24 hours post-procedure at intervals per standard of care.	
			11.9 Prior to Discharge…	…collected. • NYHA classification ~~• Neurological physical examination, which must be performed by a neurologist, neurology fellow, neurology physician assistant, or neurology nurse practitioner who is independent of the study.~~ • NIHSS,…	Updated for clarity
			11.10 Follow-up	All implanted subjects will be evaluated at 30 days, ~~6 months,~~ 12 months… Visits completed outside these windows will be recorded as protocol deviations. ~~After 6 months, visits will be scheduled on an annual basis from 1 through 5 years.~~ Each follow-up visit…	
			11.10.1 30-Day Follow-up…	• Quality of Life… **Note:** Quality of life will be evaluated by the Kansas City Cardiomyopathy and SF-12 questionnaires at baseline, 1 month, 1 year, and 5 years. A formal health economics analysis may be completed if meaningful clinical results are obtained. • Complete adverse event (AE, SAE, SADE, UADE, ADE and CEC events) assessment for test ~~and control~~ device(s) and device deficiencies assessment for test device(s), with associated treatment • For subjects in the Bicuspid Nested Registry cohort, a computed tomography scan at 30 days post LOTUS Edge Valve implantation. The CT scan must be performed per the CT Core Laboratory procedure guidelines (see study Manual of Operations) and sent to the CT Core Laboratory for independent analyses. • For subjects in the CT Imaging Substudy assessment of prosthetic valve leaflet mobility using 4D CT must be performed per the CT Core Laboratory procedure guidelines (see study Manual of Operations). All 4D CT scans for subjects enrolled in the CT Imaging Substudy must be sent to the CT Core Laboratory for independent analyses. **Note**: The CT scans will be read by the CT Core Laboratory and will not be provided to local investigators except as per below. Local reading should be done only for non-cardiac valve findings such as unexpected lung pathology. A study CT scan can be unblinded upon investigator	

Table 26.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				request based on any of the following if the event occurs within 2 weeks of the study CT scan. o Any neurological event o Any potential embolic event o Any MI (ST segment elevation MI or non-ST segment elevation MI) o Increase in aortic regurgitation to moderate or severe o A change in echocardiographic parameters including an increase in mean gradient of >10 mmHg or a change in Doppler velocity index (DVI) of >0.05. If any of the above events occurs outside of the 2 week window around the study CT scan, the investigator must not be unblinded to the core laboratory assessment of the study CT scan and instead should perform a separate CT scan if clinically indicated. If an additional CT scan is performed for clinical indications, it should be sent to the CT Core Laboratory for analysis	
			11.10.2 6-Month Follow-up…	— **(section removed)**	
			11.10.3. 12-Month Follow-up…	• Complete adverse event (AE, SAE, SADE, UADE, ADE and CEC events) assessment for test ~~and control~~ device(s) and device deficiencies assessment for test device(s), with associated treatment • Quality of Life Surveys: Kansas City Cardiomyopathy and SF-12 Quality of Life Questionnaires **Note**: Health utilities will be evaluated by the Kansas City Cardiomyopathy and SF 12 Quality of Life questionnaires at baseline, 1 month, 1 year, and 5 years. A formal health economics analysis may be completed if meaningful clinical results are obtained.	
			11.10.4 Annual Follow-up…	All implanted subjects must be evaluated… • Complete adverse event (AE, SAE, SADE, UADE, ADE and CEC events) assessment for test ~~and control~~ device(s) and device deficiencies assessment for test device(s), with associated treatment • Quality of Life Surveys: Kansas City Cardiomyopathy and SF-12 Quality of Life Questionnaires	

Table 26.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				Note: Quality of life will be evaluated by the Kansas City Cardiomyopathy and SF 12 questionnaires at baseline, 1 month, 1 year, and 5 years. A formal health economics analysis may be completed if meaningful clinical results are obtained. • For subjects enrolled in the CT Imaging Substudy, assessment of prosthetic valve leaflet mobility using 4D CT must be performed per the CT Core Laboratory procedure guidelines (see study Manual of Operations). The 4D CT scans done for the CT Imaging Substudy must be sent to the CT Core Laboratory for independent analyses. **Note:** The CT scans will be read by the CT Core Laboratory and findings will not be provided to local investigators except as noted above. Local reading should be done only for non-cardiac valve findings such as unexpected lung pathology. A study CT scan can be unblinded upon investigator request based on the conditions described in Section 11.10.1 if the event occurs within 2 weeks of the study CT scan.	
			11.10.7 Withdrawal and Replacement…	— **(separate section removed)**	
			11.10.8 Explant Procedure	**11.10.6 Explant Procedure** If a… valve ~~If a SAPIEN 3 control…~~ Information…	Updated to reflect single-arm design
			11.11 Study Completion	All subjects who receive a test ~~or control~~ device will be evaluated at 30 days, ~~6 months,~~ 12 months... For subjects who do not receive a test ~~or control~~ device, participation in the study will be considered complete after the 1-year visit. Any ongoing adverse events after study completion should be managed per standard of care.	Updated for clarity
			11.12 Source Documents	When available, original source documents (see Table 26.2 1 for definition) should be maintained at the investigational center. In lieu of original source documents, certified copies are required to be maintained. A certified copy is a copy (irrespective of the type of media used) of the original record that has been verified (i.e., by a dated signature [PI or as delegated by PI] or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original. Source documentation includes but is not limited to those items noted in Table 11.12 1. New **Table 11.12-1 Source Documentation Requirements**	

Table 26.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
			11.13 Local Laboratory/…	Appropriate certifications and documentation records are required to be maintained at the investigative center for local laboratory/vendor work.	
			12.1 Endpoints	— **(section removed)**	Updated for single-arm design
			12.1.1 Primary Endpoint	The primary endpoint is the composite of all-cause mortality, and all stroke ~~and mild or greater paravalvular aortic regurgitation (PVR; based on core lab assessment)~~ at 1 year.	
			12.1.1.1 Statistical Hypothesis for the Primary Endpoint	~~*12.1.1.1.1 Primary Hypothesis for the Primary Endpoint*~~ The statistical hypothesis is that the rate of the primary endpoint (composite of all-cause mortality and all stroke at 1 year) in the Main Cohort is less than the performance goal (PG) of 15.2% (expected rate of 11.1% plus testing margin of 4.1%). A one-sample z-test will be used to test the one-sided hypothesis that the 1-year primary endpoint rate for LOTUS Edge in the Main Cohort is less than the PG: H_0: $P_{LOTUS\ Edge} \geq PG$ H_1: $P_{LOTUS\ Edge} < PG$ where $P_{LOTUS\ Edge}$ is the primary endpoint rate for the LOTUS Edge group and PG is the performance goal. The primary analysis set for the primary endpoint is the intention-to-treat (ITT) analysis set (see Section 12.2.1). This endpoint will also be analyzed for the implanted analysis set.	
			12.1.1.1.2 Secondary Hypothesis…	— **(section removed)**	
			12.1.1.2 Sample Size Parameters for the Primary Endpoint	The sample size calculation for the primary endpoint is based on the following assumptions. • Expected rate for LOTUS Edge = 11.1%* • Testing margin = 4.1% (37% relative to the expected rate) • Performance goal (PG) = 15.2% (expected rate of 11.1% plus testing margin of 4.1%) • Test significance level (α) = 0.025 (1-sided) • Power (1 minus ß) = 87.5% • Number of evaluable subjects = 675 • Expected rate of attrition = 3%	

Table 26.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				• Total enrollment (evaluable Main Cohort) = 696 * Estimated pooled rate from the fixed/random effects model based on the ITT TAVR arm data from PARTNER II S3i and SURTAVI	
			12.1.1.2.2 Secondary Hypothesis…	— **(section removed)**	
			12.1.1.3 Success Criteria-Primary Endpoint	If the *P* value from the one-sample z-test is <0.025, it will be concluded that the primary endpoint with the LOTUS Edge Valve System is less than the PG. This corresponds to the one-sided upper 97.5% confidence bound of the observed composite rate of all-cause mortality and all stroke in the Main Cohort at 1 year being < 15.2%.	
			12.1.1.4 Statistical Methods-Primary Endpoint	All subjects who are enrolled ~~and randomized~~ will be eligible for evaluation. ~~Any events or hospitalizations occurring after enrollment but prior to the index procedure should be entered in the electronic data capture system.~~ Handling of dropouts and missing data will depend on their frequency and the nature of the outcome measure. Sensitivity analyses (e.g., tipping-point analysis) will be performed to assess the impact of subjects with inadequate follow-up (i.e., missing data) on the primary endpoint and to assess the robustness of the conclusion of the primary analysis. ~~A sensitivity analysis of the primary endpoint, including events occurring after enrollment but prior to the index procedure, will be performed. This sensitivity analysis of the primary endpoint will include the last available post-procedure core lab assessment of PVR data for subjects who survive with no stroke through 1 year but have missing or unanalyzable data for PVR at 1 year.~~ Statistical models…	Updated for clarity
			12.1.2 Secondary Endpoint	— **(section removed)**	Updated to reflect single-arm design and for clarity
			12.1.3 Baseline Comparability	Baseline data will be summarized ~~by treatment group for the randomized subjects~~ and separately for subjects in the Main Cohort, Roll-In Cohort, and Bicuspid Nested Registry cohort. Subject demographics… variables. ~~Treatments for the randomized subjects will be compared with a chi-square or Fisher exact test for discrete variables and a Student t test for continuous variables.~~ Procedural characteristics will be summarized similarly.	

Table 26.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
			12.1.4 Post-procedure Measurements	**12.1.3 Post-procedure Measurements** Post-procedure information… will be presented. ~~Treatments for the randomized subjects will be compared with the chi-square or Fisher exact test for discrete variables and the Student t-test for continuous variables. No inferences are planned on the additional measurements and, therefore, alpha-adjustments for multiple comparisons will not be used.~~ The Kaplan-Meier… estimate rates for time-to-event endpoints ~~and treatment groups will be compared using the Log-rank and Wilcoxon tests~~. Adverse…	
			12.1.5 Subgroup Analyses for Randomized Subjects	**12.1.4 Subgroup Analyses** Primary and pre-specified additional endpoints… as appropriate. For the CT Imaging Substudy, data from the 4D CT scan at 30 days and at 1 year post LOTUS Edge valve implantation to assess the prevalence of reduced leaflet mobility will be summarized and the relationship, if any, to clinical events will be explored.	Updated for clarity and for the CT Imaging Substudy
			12.2.1 Analysis Sets	The primary endpoints and additional measurements will be analyzed on an intention-to-treat (ITT)~~, an as-treated~~ and an implanted basis. ~~Among the randomized cohort,~~ For ITT analyses, all subjects who sign the IRB/HREC-approved study ICF (see Section 11.3) and are enrolled in the trial ~~and are randomized~~ will be included in the analysis, whether or not an ~~assigned~~ study valve ~~(LOTUS Edge Valve or SAPIEN 3 Valve)~~ was implanted. ~~The as-treated … control subject for the as-treated analyses).~~ For implanted analyses, ITT subjects who had the ~~assigned, randomized~~ study valve ~~(LOTUS Edge Valve or SAPIEN 3 Valve)~~ implanted will be included in the analysis. ~~For all analysis sets, if a subject…~~ For the Main Cohort, the primary endpoint ~~(both hypotheses) and the secondary endpoint~~ will be analyzed for the ITT, ~~as-treated,~~ and implanted analysis sets. The primary analysis for the primary endpoint ~~(both hypotheses) and the secondary endpoint~~ will be based on the ITT analysis set.	Updated to reflect single-arm design
			12.2.3 Randomization…	— **(section removed)**	
			12.2.4 Reporting Events	**12.2.3 Reporting Events** For all ~~randomized~~ subjects, ~~events from the time of randomization onward~~ all events that occur from the time of enrollment will be reported. ~~For randomized subjects…~~ For time based clinical events, the cut-off for	

Table 26.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				events for 30-day endpoints will be 30 days, ~~for 6-month endpoints will be 180 days,~~ for 1-year endpoints…	
			12.3 Data Analyses	Baseline and… analysis of the primary ~~safety~~ endpoint~~, primary effectiveness endpoint, secondary endpoint,~~ and additional measurements.	
			12.3.2 Interim Analyses	…or futility. Administrative analyses for regulatory agency review may be performed.	Updated for clarity
			12.3.3 Justification of Pooling	All analyses ~~for the primary endpoint~~ will be ~~presented~~ performed using data pooled across clinical centers. An assessment… made by fitting a logistic regression model with the primary composite endpoint of all death and all stroke and with the center as the main effect. If the *P* value for the coefficient for the center is ≥0.1, the data can be pooled across centers. In the analysis… centers with fewer than 10~~6~~ subjects enrolled… have ≥10~~6~~ subjects, but…	
			12.3.4 Multivariable…	Univariate and multivariate analyses will be performed to assess the effect of potential predictors on the primary endpoint ~~and the secondary endpoint~~ as described…	
			13.1 Data Collection…	The clinical database will reside on a production server hosted by Medidata EDC System (New York, New York, USA). All,,,	
			13.2 Data Retention	The Principal Investigator or his/her designee or Investigational center will maintain all essential study documents and source documentation that support the data collected on the study subjects in compliance with applicable regulatory requirements. Documents... The Principal Investigator or his/her designee will take measures to ensure that these essential documents are not accidentally damaged or destroyed. If for any reason the Principal Investigator or his/her designee withdraws responsibility for maintaining these essential documents, custody must be transferred to an individual who will assume responsibility and BSC must receive written notification of this custodial change. Centers are required to inform BSC in writing where paper or electronic files are maintained in case files are stored off site and are not readily available.	
			13.3.4 Histopathology…	If a LOTUS Edge valve ~~(test device)~~ is explanted…	
			15. Deviations	An Investigator…	

Table 26.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				Deviations will be reviewed and evaluated on an ongoing basis and, as necessary, appropriate corrective and preventive actions (including IRB/HREC notification, center re-training, or center discontinuation/termination) will be put into place by the Sponsor.	
			16 Device Accountability	**16.1 Device Accountability for Products Labelled Investigational** The ~~LOTUS Edge™ Valve System and iSleeve™ Introducer Set~~ investigational devices will be released by the Sponsor or designee to the clinical center only after the center has been initiated and all regulatory approvals as well as required documentation have been collected from the center. The ~~LOTUS Edge™ Valve System and iSleeve™ Introducer Set~~ investigational devices shall be securely maintained and controlled and used only in this clinical study. Additionally, the study personnel must follow the instructions related to the storage of the ~~test and control~~ investigational devices as noted in the corresponding IFUs. ~~Device Accountability Logs for the LOTUS Edge Valve System and iSleeve Introducer will be provided to the centers and will be used to track subjects and device allocations during the study.~~ An electronic interactive response technology (IRT) will be used for investigational device management and accountability during the study. The Sponsor or designee shall keep records to document the physical location of all investigational devices from shipment of the investigational devices to the investigation centers until return or disposal. The IRT will be used to document reception of the investigational device at a center. Records shall be kept by authorized center study personnel to document the physical location and conditions of storage of all investigational devices. Centers must not dispose of any investigational devices for any reason at the center unless instructed to do so by BSC. Any investigational device that is disposed of at the center must be documented appropriately. ~~recorded in the Device Accountability Log. The PI~~ Centers must document the reasons for any discrepancy noted in device accountability. The Principal Investigator or an authorized designee shall keep records documenting the receipt, use, return, transfer, and disposal of the investigational devices, which shall include the following; this will be verified by personnel from BSC or its designee. • Date of receipt at the center	

Table 26.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				• Identification… • Date of return and quantity of unused…	
			16.2 Control Device	**16.2 Commercial Device** For countries where the introducer sets are commercially available, appropriate information on the ~~SAPIEN 3 control~~ device size and model…	
			17.1 Statement of Compliance	The REPRISE IV study will be conducted in accordance with 21 CFR 814.20 parts 11, 50, 54, 56, and part 812… The study… appropriate. Also, the study shall not begin prior to issuance of the center Authorization to Screen, as provided by the Sponsor. Any…	
			17.2 Investigator Responsibilities	The Principal Investigator of an investigational center is responsible for ensuring that the study is conducted in accordance with the Clinical Study Agreement, the clinical investigation plan/protocol… • Provide… results… ~~• Complete training requirements associated with the SAPIEN 3 device…~~ • Record, report… adverse event as applicable per the protocol and observed device deficiency. • Report to BSC, per the protocol requirements, all SAEs and device deficiencies that could have led to a SADE and potential/USADE or UADE. • Report to the IRB/HREC and regulatory authorities any SAEs and device deficiencies that could have led to a SADE and potential/USADE or UADE, if required by applicable laws ~~the national~~ or regulations or this protocol... • Allow… be accessible to the clinical research monitor or auditor and respond to questions during monitoring visits or audits... • Ensure that informed consent is obtained in accordance with applicable laws, this protocol and local IRB/HREC requirements... • Provide the subject with well-defined procedures for possible emergency situations related to the clinical study, and make the necessary arrangements for emergency treatment, including decoding procedures for blinded/masked clinical investigations, as needed.	

Table 26.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
			17.2.1 Delegation of Responsibility	…providing appropriate training so the delegate is competent to perform the tasks they have been delegated, and adequate supervision of those to whom tasks are delegated. Where there is a sub-investigator at a center, the sub-investigator should not be delegated the primary supervisory responsibility for the center. The investigator…	
			17.3 Institutional Review Board	**17.3 Institutional Review Board/Human Research Ethics Committee** ~~Prior to gaining Approval-to-Enroll status the investigational center will provide to the Sponsor documentation verifying that their IRB is registered or that registration has been submitted to the appropriate agency, as applicable according to national/regulatory requirements.~~ The investigational center will obtain the written and dated approval/favorable opinion of their IRB/HREC for the clinical investigation before recruiting subjects and implementing all subsequent amendments, if required. A copy… investigational product~~/equipment~~... Any amendment to the protocol will require review and approval by the IRB/HREC before the changes are implemented in the study. All changes to the ICF will be IRB/HREC approved; a determination will be made regarding whether a new ICF needs to be obtained from subjects who provided consent using a previously approved ICF. Annual IRB/HREC approval and renewals will be obtained throughout the duration of the study as required by applicable local/country laws or regulations or IRB/HREC requirements. Copies of the Investigator's reports and the IRB/HREC continuance of approval must be provided to the Sponsor.	
			17.4 Sponsor Responsibilities	All information… considered confidential by BSC and will be kept confidential in accordance with all applicable laws and regulations. Only… research and/or other business purposes such as overseeing and improving the performance of its device, new medical research and proposals for developing new medical products or procedures. All data used in the analysis and reporting of this study or shared with a third-party researcher will be without identifiable reference to specific subjects… Boston Scientific Corporation will keep subjects' health information confidential in accordance with all applicable laws and regulations. ~~Boston Scientific Corporation may use subjects' health information to~~	

Table 26.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				~~conduct this research, as well as for additional purposes, such as overseeing and improving the performance of its device, new medical research and proposals for developing new medical products or procedures, and other business purposes~~. Information…	
			17.4.1 Training with the Investigational…	Training on the LOTUS Edge Valve System has been developed that meets the requirements of ISO 5840-3 and includes the following elements. ~~• Device Description: A detailed description of all components of the device including a summary of the basic principles of operation.~~ ~~• Patient selection and sizing: A detailed review of pre-procedural imaging techniques to aid in patient selection and sizing decisions for valve implantation.~~ ~~• Step by Step Procedure: A detailed description of each step of the procedure. The training describes any warnings associated with any steps, and tips and tricks for valve implantation.~~ ~~• Implantation techniques: A detailed review of specific implantation techniques based on clinical cases.~~ ~~• Device Demonstration: A hands on training to practice the implantation procedure in a bench model or a robotic simulation system.~~ • Device training to include a detailed description of all device components including a summary of the basic principle of operation and hands-on bench top demonstration using valve and delivery system components in a simulated implantation model. • Patient selection and device sizing to include a review of the Directions for Use (IFU) and pre-procedural and procedural imaging techniques to aid in sizing decisions and implantation of the valve • Implantation techniques to include a step-by-step review of the procedure (including alternative access, where applicable) while highlighting associated cautions and warnings from the IFU. Training should include video representation of implantation	

Table 26.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				procedural steps and associated fluoroscopic images of each step. Clinical case reviews should be presented to demonstrate intended procedural steps as well as appropriate troubleshooting. • Proctoring: The investigator and co-investigators as well as the scrub team will be proctored by an experienced TAVR physician on a minimum of 5 ~~6~~ implantation procedures. ~~These are to be performed in the investigator's institution with his/her staff.~~ If the proctor or investigators (First Operator and Second Operator) are not satisfied that these initial proctored procedures are sufficient preparation, then subsequent proctoring sessions may be added as needed. ***Note 1*:** ~~The training requirements listed above apply to centers that do not have any previous~~ If a physician has prior experience implanting the Lotus Valve, he/she will be trained per above to the LOTUS Edge Valve System prior to re-starting first implants. ~~If the center has prior experience implanting the Lotus Valve but not the LOTUS Edge Valve System, the training will be modified to focus on the changes between Lotus and LOTUS Edge. These Lotus-experienced physicians will not be certified to the LOTUS Edge Valve System until these training requirements have been met and three implants with the LOTUS Edge Valve System have been completed.~~ Further, if the physician was considered proctor-free under the previous Lotus program, a proctor will not be required **Note 2:** For centers that do not have implantation experience with the LOTUS Edge Valve System, at least 2 roll-in cases will be performed before enrollment can commence in the ~~Randomized~~ Main Cohort … will count towards the 5 ~~6~~ required proctored…	
			17.4.2 Role of Boston Scientific…	Boston Scientific Corporation personnel (including field clinical engineers) who are trained in the use of the investigational device will... trained on the investigational device(s) IFU(s). Support may include HCP training (see Section 17.4.1), addressing HCP questions, or…	
			18 Monitoring	… In addition, the clinical research monitor verifies… and that the Principal Investigator continues to have sufficient staff and facilities to conduct the study safely and effectively. The Principal	

Table 26.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				Investigator/institution guarantees direct access to original source documents and/or certified copies (please see Section 11.12) by BSC … It is important that the Principal Investigator and relevant…	
			19 Potential Risks and Benefits	Risks to clinical subjects… the Evolut R CE Mark Study, the Surgical Replacement and Transcatheter Aortic Valve Implantation (SURTAVI) trial, the EVOLUT R US study, the PORTICO Pre-CE Mark study, and the… Potential risks and benefits have been included in the study-specific template of the ICF provided to the study centers (see Section 21). ~~While some risks may be lower with SAPIEN 3 compared to LOTUS Edge (e.g., new conduction disturbance that may result in the need for a permanent pacemaker), there may also be potential benefits of the LOTUS Edge Valve over SAPIEN 3 (e.g., a lower likelihood of PVR and a lower likelihood of annular rupture or valve malpositioning).~~	Updated to reflect single-arm design and to include additional references
			19.1 Risks Associated with…	**19.1 Anticipated Adverse Events and Risks Associated with…** Adverse events… use of the LOTUS Edge Valve System, and the Lotus and iSleeve Introducer Sets ~~and/or SAPIEN 3~~ include but may not be limited to the following. • Abnormal lab values (including anemia, electrolytes, hemolysis and/or hemolytic anemia) • Access site complications (including arteriovenous [AV] fistula, hematoma or lymphatic problems) •Allergic reaction (including to medications, anesthesia, contrast, or device materials, including nickel, titanium, tantalum, bovine-derived materials or polyurethanes) •Bleeding or hemorrhage (possibly requiring transfusion or ~~intervention~~ additional procedure) •Cerebrovascular accident, stroke, transient ischemic attack or cerebral infarction including asymptomatic neuroimaging findings • Device misplacement, migration, or embolization • Emboli (including air, ~~calcium,~~ tissue, thrombus or device materials) • Endocarditis… • Fever or inflammation… ~~• Hemolysis and/or hemolytic anemia…~~ • Infection (local and/or systemic~~, including septicemia~~)	Updated for clarity

Table 26.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				~~• Inflammation~~ • Mitral valve insufficiency • Myocardial ~~ischemia or~~ infarction • Nerve injury or neurologic deficits (including encephalopathy) • Pericardial effusion or ~~cardiac~~ tamponade… • Restenosis (including pannus formation) • Valve dysfunction… As a result of these ~~complications~~ adverse events, the subject may require medical, percutaneous or surgical intervention, including re-operation and replacement of the valve. ~~Such complications may be~~ These events may lead to fatal outcomes. As the LOTUS Edge Valve System ~~and the iSleeve Introducer Set are~~ is an investigational device, uncertainty… **19.2 Risks Associated with the Study Device(s)** Overall, there are no incremental risks expected with the investigational device(s) compared to similar devices on the market.	
			19.4 Risk Minimization Actions	**19.5 Risk Minimization Actions** Additional risks… Neurological assessments (NIHSS and mRS) will be performed…	
			19.6.1 Potential Benefits…	…as described in the scientific literature (see summary in Section 4.1 of this document and details in ~~Sections 2 and 3 of~~ the Investigator Brochure), potentially…	Updated for clarity
			20.1 Reportable Events…	It is the responsibility… • Unanticipated adverse device effects/unanticipated serious adverse device effects… • If complications or… ~~For the randomized cohort event reporting (eCRF data entry) is required beginning from the time of randomization.~~ ~~For the roll-in cohort and the Bicuspid Nested Registry cohort, event reporting…~~ Event reporting… Refer to Section 19 for the known risks associated with the study devices ~~(test and control)~~…	Updated for clarity to reflect the single-arm design

Table 26.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
			20.2 Definitions and Classification	Adverse event definitions are provided in Table 20.2 1. Administrative edits were made on the safety definitions from ISO 14155 and MEDDEV 2.7/3 for clarification purposes. **Table 20.2-1: Adverse Event Definitions** Any untoward medical occurrence… **Note 1:** This definition includes events related to the investigational medical device ~~or the comparator~~.	
			Table 20.2… Serious Adverse Event Definition	**Note 1:** This definition meets the reporting objectives and requirements of ISO 14155 and MEDDEV 2.7/3. Adverse event that: …or 3) in-patient hospitalization or prolongation of existing hospitalization, or… **Note 2:** Planned hospitalization for a pre-existing condition, or a procedure required by the ~~protocol~~ clinical investigational plan, without a serious deterioration in health, is not considered a serious adverse event.	Changed to address updated regulatory requirements
			Table 20.2… Unanticipated Serious Adverse Device Effect (USADE) Definition	Added text: Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report. **Note**: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.	Updated for clarity
			20.3 Relationship to Study Device(s)	The Investigator must assess the relationship of the AE/SAE to the study device and procedure… **Table 20.3-1:** Criteria for Assessing Relationship of Study Device and Procedure to Adverse Event	
			20.4 Investigator Reporting Requirements	The communication requirements… event. ~~Centers should report control device related deficiencies as per requirements in the control device IFU.~~ **Table 20.4 1: Investigator Reporting Requirements**	Updated requirements

Table 26.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes			Justification for Changes
				Unanticipated Adverse Device Effect/Unanticipated Serious Adverse Device Effect (UADE/USADE)	Complete adverse event (AE) electronic case report form (eCRF) page with all available new and updated information	• Within 1 business day of first becoming aware of the event • ~~Beginning from time of enrollment for all subjects~~ • Terminating at the end of the study	
					Provide ~~copies of~~ all relevant source documentation (de-identified/ pseudonymized) for reported event ~~requested by BSC~~	• At request of Sponsor	
				Serious Adverse Event (SAE) ~~including Serious Adverse Device Effects (SADE)~~	Complete AE eCRF page with all available new and updated information	• Within 3 calendar days of first becoming aware of the event or as per local/regional regulations. • ~~Beginning from time of enrollment for all subjects~~ • Reporting required through the end of the study	
					Provide all relevant source documentation (de-identified/ pseudonymized) for reported event	• ~~When documentation is available~~ At request of Sponsor	

Table 26.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes			Justification for Changes
				Serious Adverse Device Effects (SADE)	Complete AE eCRF page with all available new and updated information.	• Within 3 calendar days of first becoming aware of the event or as per local/regional regulations. • Reporting required through the end of the study	
					Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• When documentation is available • At Sponsor request.	
				Adverse Event including Adverse Device Effects (AE/ADE)	Complete AE eCRF page, which contains such information as date of AE, treatment of AE resolution, assessment of seriousness and relationship to the device.	• ~~As soon as possible before the next planned monitoring visit~~ In a timely manner (e.g., recommend within 10 business days) after becoming aware of the information ~~• Beginning from time of enrollment for all subjects~~ • Reporting required through 12 months	
					Provide all relevant source documentation (de-identified/	• At request of Sponsor	

Table 26.1-1: Protocol Revision History

<table>
<tr><th>Revision Version</th><th>Protocol Date</th><th>Template Number and Version</th><th>Protocol Sections Modified</th><th colspan="3">Summary of Changes</th><th>Justification for Changes</th></tr>
<tr><td rowspan="5"></td><td rowspan="5"></td><td rowspan="5"></td><td rowspan="4"></td><td></td><td>pseudonymized) for reported event.</td><td></td><td rowspan="4"></td></tr>
<tr><td>Device Deficiencies (including but not limited to failures, malfunctions, and product nonconformities)
Note: …</td><td>Complete ~~applicable~~ eCRF ~~fields/~~page with all available new and updated information.</td><td>~~Investigational Device~~
• Within 3 calendar days of first becoming aware of the event
• Reporting required through 12 months
~~Control Device~~
~~As required per IFU and as per local/regional regulations~~</td></tr>
<tr><td>Provide all relevant source documentation (de-identified/ pseudonymized) for reported event</td><td>• At request of Sponsor</td></tr>
<tr><td colspan="3">Note: The… device.
Please note that pre-market studies are clinical studies with investigational devices or with medical devices that bear the regulatory approval and are not being used for the same approved indications.</td></tr>
<tr><td>20.5.1 Boston Scientific Device Deficiencies</td><td colspan="3">All ~~LOTUS Edge Valve System and iSleeve Introducer Set~~ device deficiencies (including but not limited to failures, malfunctions, use errors, product nonconformities, and inadequacy in the information supplied by the manufacturer) related to the investigational device or future iterations must be documented…</td><td>Updated for clarity</td></tr>
<tr><td>20.5.2 Control Device Deficiencies</td><td colspan="3">—
Section removed</td><td>Updated single-arm trial design</td></tr>
<tr><td>20.6. Reporting to Regulatory</td><td colspan="3">20.6. Reporting to Regulatory Authorities / IRBs/ HRECs / Investigators</td><td>Updated for clarity</td></tr>
</table>

Table 26.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
			Authorities / IRBs/ Investigators	… Boston Scientific Corporation is responsible for reporting AE information to all participating Principal Investigators, IRBs/HRECs, and regulatory authorities as applicable according to local reporting requirements. The Principal Investigator is responsible for informing the IRB/HREC and regulatory authorities of UADEs, SADEs, SAEs, Device Deficiencies and/or other CEC events as applicable according to local reporting requirements. ~~A copy of the Investigator's reports and other relevant reports (if applicable) to the IRB/HREC must be provided to BSC in accordance with local requirements.~~	
			21 Informed Consent	Subject participation in this clinical study is voluntary. Informed Consent is required from each subject or his/her legally authorized… … and the local Ethics Committee and/or Regulatory authority body, as applicable… The ICF shall always be signed and personally dated by the subject or legal representative competent to sign the ICF under the applicable laws, rules, regulations and guidelines and by the investigator or... Failure to obtain subject consent will be reported by BSC to the applicable regulatory body according to their requirements (e.g., the United States Food and Drug Administration [FDA] requirement is within 5 working days of learning of such an event). Any violations of the informed consent process must be reported as deviations to the Sponsor and local regulatory authorities (e.g., IRB/HREC), as appropriate… … such as if there are amendments to the applicable laws, protocol, a change in Principal Investigator, administrative changes, or following annual review by the IRB/HREC. The new version of the ICF must be approved by the IRB/HREC. Boston Scientific Corporation approval is required if changes to the revised ICF are requested by the center's IRB/HREC. The IRB/HREC will determine the subject population to be re-consented. Study personnel should explain that even if a subject agrees to participate in the study and signs an ICF, the heart team and/or the CRC may determine that the subject is not a suitable candidate for the study and/or TAVR procedure. A confidential Screening/Enrollment Log will be	

Table 26.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				maintained by the center to document select information about candidates who fail to meet the general or "other specific" entry criteria.	
			22.1 Safety Monitoring Process	…During regularly scheduled monitoring visits, clinical research monitors will support the dynamic reporting process through their review of source document and other data information….	
			23.2 Termination of…	Any investigator or associated IRB/HREC in the REPRISE IV study or regulatory authority may discontinue participation…	
			23.4 Criteria for Suspending/…	… In the event of termination of ~~investigator~~ center participation, all study devices and testing equipment, as applicable, will be returned to BSC unless this action would jeopardize the rights, safety or well-being of the subjects. The IRB/HREC and regulatory authorities, as applicable, ~~should~~ will be notified. ~~All subjects enrolled in the study at the center will continue to be followed per this protocol. The Principal Investigator at the center must make provision for these follow-up visits unless BSC notifies the investigational center otherwise.~~ Study subjects will be contacted, as applicable, and be informed of changes to study visit schedule.	
			24 Publication Policy	~~In accordance with the Global SOP – Human Subject Data and Research Controls,~~ Boston Scientific Corporation requires disclosure of its involvement as a sponsor or financial supporter in any publication or presentation relating to a BSC study or its results. ~~In accordance with the Global SOP – Human Subject Data and Research Controls,~~ Boston Scientific Corporation will submit study results for publication (regardless of study outcome~~) in a timely manner~~ following the conclusion or termination of the study. Boston Scientific Corporation ~~follows authorship principals as~~ adheres to the Contributorship Criteria set forth in the Uniform Requirements… …The data, analytic methods, and study materials for this clinical trial may be made available to other researchers in accordance with the Boston Scientific Data Sharing Policy (http://www.bostonscientific.com/en-US/data-sharing-requests.html).	
			25 Bibliography	Bibliography updated to accommodate new references in the Introduction, etc.	
			26.2 Definitions	**Table 26.2-1 Definitions** Removed "AS-TREATED ANALYSIS SET"	

Table 26.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes		Justification for Changes
				IMPLANTED ANALYSIS SET	This population includes all subjects who sign the IRB/HREC-approved study Informed Consent Form, are enrolled in the trial, and are implanted with the ~~assigned, randomized~~ study ~~device~~ valve. ~~Note 1: If a subject receives 2 valves, the subject is assigned to the group corresponding to the first valve received.~~	
				INTENT TO TREAT (ITT) ANALYSIS SET	This population includes all subjects who sign the IRB/HREC-approved study Informed Consent Form and are enrolled in the trial ~~and are randomized~~ whether or not a ~~assigned~~ study device is implanted. ~~Subjects in the ITT population will be followed with their ITT cohort.~~ ~~Note 1: If a subject receives 2 valves, the subject is assigned to the group corresponding to the first valve received.~~	
				OPERATIVE RISK	Operative risk is determined by a center cardiac surgeon and must be confirmed by the Case Review Committee (including a cardiac surgeon). ~~**Intermediate:** Estimated 30-day risk of mortality is 3–10%~~ ~~**High:** Estimated 30-day risk of mortality is >10–15%%~~ ~~**Very High:** Estimated 30-day risk of mortality is >15%~~ ~~**Extreme:** Estimated 30-day risk of irreversible morbidity or mortality is ≥50%~~	
			27.1.2 Protocol Version B to Version C	Table 27.1-2 lists changes between protocol versions B and C. **Table 27.1-2: Table of Changes for REPRISE IV Protocol Version C (Compared to REPRISE IV Protocol Version B)**		

Table 26.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes		Justification for Changes
D	21-Nov-2018	90702637 Rev/Ver AG	Page 2	Study Coordinating Principal Investigators	*Interventional Cardiologist Study Co-Principal Investigator* Christopher U. Meduri, MD, MPH Piedmont Heart Institute 95 Collier Road Northwest, Suite 5015 Atlanta, GA 30309 ~~Ted Feldman, MD~~ ~~Evanston Hospital, North Shore University Health System~~ ~~Cardiology Division - Walgreen Building 3rd Floor~~ ~~2650 Ridge Avenue~~ ~~Evanston, IL 60201 USA~~	New Study Coordinating Principal Investigator
					Bicuspid Registry – Coordinating Principal Investigator Vivek Rajagopal, MD Piedmont Heart Institute 95 Collier Road Northwest, Suite 5015 ~~1968 Peachtree Road, NW, Building 95, Suite 5015~~ Atlanta, GA 30309 USA	Updated address
				Current Version: 21-Nov-2018 Updated Table of Revision History		Updated for clarity
			11.2 Study Candidate Screening	… Clinical assessment and evaluation, collected tests and images (e.g., echocardiography, computerized tomography [CT], angiography) performed in preparation for TAVR~~, any planned concomitant treatment of coronary artery disease (CAD),~~ and any planned…		Concomitant treatment of coronary artery disease is not allowed
			16.1 Device Accountability for Products Labeled Investigational	…all unused investigational devices must be returned to BSC or its designee. ~~A copy of the Device Accountability Logs must also be provided to BSC.~~		All Device Accountability records to be logged electronically with no separate Device Accountability Logs

Table 26.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
			27.1.3 Protocol Version C to Version D	Table 27.1-3 lists changes between protocol versions C and D. **Table 27.1-3: Table of Changes for REPRISE IV Protocol Version D (Compared to REPRISE IV Protocol Version C)**	Updated for clarity
E	25-Feb-2020	90702637 Rev/Ver AG	Page 2	Current Version: 25-Feb-2020 Updated Table of Revision History	Updated for clarity
			2. Synopsis, Study Design	Updated REPRISE IV Study Design Overview figure to show follow-up to 10 years post index procedure.	FDA request to extend study to 10 years

			2. Synopsis, Additional Measurements	Additional measurements… will be collected… and annually through 10 years post index procedure…
				• Safety endpoints…
				  ○ Bleeding: Life-threatening… (through 5 years)
				  ○ Major vascular complication (through 5 years)
				• Additional indications of prosthetic aortic valve performance as measured by transthoracic echocardiography (TTE; see **Note 2** and **Note 3** below)
				• Functional… (see **Note 3** below)
				• Neurological… (see **Note 4** below)
				Note 3: Echocardiography and NYHA assessment are not required in years 6, 8, and 9 (telephone follow-up only).
				Note 4: NIHSS is required at discharge and 1 year; mRS is required at all follow-up visits up to 5 years.	

			2. Synopsis, Follow-up Schedule	All subjects implanted… and then annually for up to 10 years post-procedure… The visits at 30 days, 1–5 years, 7 years, and 10 years are to be an office/clinical or in-person visit but may be done in-hospital should the subject be admitted at the time. Telephone follow-up is allowed at 6, 8, and 9 years.	
			2. Synopsis, Study Duration	Enrollment…approximately 24 months…the total study duration is estimated to be approximately 12 years.	
			2. Synopsis, Participant Duration	… study duration for each subject is estimated to be approximately 10 years.	
			7.2 Additional Measurements	Additional measurements… collected… annually up to 10 years post index procedure… • Safety endpoints…	Updated for clarity

Table 26.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				○ Bleeding: Life-threatening… (through 5 years) ○ Major vascular complication (including annular rupture; through 5 years) • Neurological status… modified Rankin Scale… visits up to 5 years **Note 5:** Echocardiography and NYHA assessment are not required in years 6, 8, and 9 (telephone follow-up only).	
			7.3 Overview of Objectives…	Table 7.3-1 Safety measures at discharge, 30 days, and annually up to 10 years post index procedure	FDA request to extend study to 10 years
			8.1 Scale…	All subjects implanted will be followed… annually for up to 10 years post-procedure.	
			8.3 Study Design…	All implanted subjects will be followed for up to 10 years post index procedure.	
			10.3 End of Study Definition	… All subjects who receive a study device will be evaluated at discharge or 7 days (whichever comes first), 30 days, and annually up to 10 years post index procedure. Visits at 30 days, 1–5 years, 7 years and 10 years are office/in-person visits. Telephone follow-up is allowed at 6, 8, and 9 years. A subject's participation in the study will be considered complete after the 10-year visit.	
			11.1 Data Collection	Figure 11.1-1 REPRISE IV Data Collection Scheme updated to show extension of study to 10 years post index procedure Table 11.1-1 Study Event Schedule updated to show extension of study to 10 years post index procedure	
			11.1 Data Collection	Figure 11.1-1 REPRISE IV Data Collection Scheme : In the "Clinical & Anatomic Eligibility Criteria Assessment" column added "/CT Coronary Angiogram" to the "Coronary Angiogram" box Table 11.1-1 Study Event Schedule : Assessment: Coronary angiogram/CT coronary angiogram Footnote k: A coronary angiogram/CT coronary angiogram must be performed…	Clarify that CT angiogram can be used for coronary assessment, which reflects current standard of care

Table 26.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
			11.2 Study Candidate Screening	Subjects will be… ~~In the United States, the Centers for Medicare and Medicaid Services (CMS) require independent evaluations by 2 cardiac surgeons for reimbursement.~~ The heart team…	Change to CMS requirements
			11.4 Screening Assessments	Risk assessments: Society of Thoracic Surgeons (STS) score.... ~~In the United States, CMS requires independent evaluations by 2 cardiac surgeons for reimbursement.~~	
			11.4 Screening Assessments	• Imaging Assessments A coronary angiogram/CT coronary angiogram must..	Reflects current standard of care
			11.10 Follow-up	All implanted subjects will be evaluated at 30 days and then annually up to 10 years post index procedure... Physical clinic visits or in-person follow-up visits are scheduled for appointed times after the date of the procedure through 5 years and at 7 and 10 years. Telephone follow-up is allowed at 6, 8, and 9 years. Visits/telephone follow-up not completed will be considered missed and recorded as protocol deviations. Visits/telephone follow-up completed outside these windows will be recorded as protocol deviations. Each follow-up visit must be performed…	FDA request to extend study to 10 years
			11.10.3 Annual Follow-up (±45 Days)	Added "to 5 Years" to the section title All implanted subjects must be evaluated in person at 24, 36, 48, and 60 months…	Updated for clarity
			11.10.4 Follow-up (±60 Days) at 7 and 10 Years	Added new section 11.10.4 All implanted subjects must be evaluated in person at 84 and 120 months after the index procedure, with a window of ±60 days. The following assessments must be completed. The REPRISE IV eCRFs identify the specific data points to be collected. • NYHA classification • Current antiplatelet, anticoagulant (if applicable) • TTE, including assessment of effective orifice area, peak and mean aortic valve gradient pressure, aortic regurgitation assessment, peak aortic velocity, and LVEF per the Echocardiography Core Laboratory procedure guidelines. All TTEs must be forwarded to the Core Laboratory for	FDA request to extend study to 10 years

Table 26.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				independent analyses. **Note:** TTE must be done for all subjects who have a transcatheter valve implanted in the aortic position during the index procedure. • Serious adverse event (SAE, SADE, UADE, and relevant VARC events to be adjudicated by the CEC) assessment for test device(s) and device deficiencies assessment for test device(s) with associated treatment. **Note:** Relevant VARC events to be adjudicated by the CEC include the following: mortality, stroke, spontaneous myocardial infarction, acute kidney injury, repeat procedure for valve-related dysfunction, hospitalization for valve-related symptoms or worsening congestive heart failure (NYHA III or IV), new pacemaker, new onset atrial fibrillation or atrial flutter, prosthetic aortic valve malpositioning (valve migration, valve embolization, or ectopic valve deployment), TAV-in-TAV, prosthetic aortic valve thrombosis and endocarditis…	
			11.10.5 Follow-up (±60 Days) at 6, 8 and 9 Years	Added new section 11.10.5 All implanted subjects must be evaluated at 72, 96, and 108 months after the index procedure, with a window of ±60 days. This evaluation may be conducted by telephone. The following assessments must be completed. The REPRISE IV eCRFs identify the specific data points to be collected. • Current antiplatelet, anticoagulant (if applicable) • Serious adverse event (SAE, SADE, UADE, and relevant VARC events to be adjudicated by the CEC) assessment for test device(s) and device deficiencies assessment for test device(s) with associated treatment. Please see Section 11.10.4 for a list of relevant VARC events.	
			11.10.6 Management of Missed…	NOTE: Updated section number from 11.10.4 to 11.10.8 Missed or late visits (or telephone follow-up as indicated in Table 11.1 1) will be recorded as protocol deviations and will be reviewed as such by the Sponsor or designee on a regular basis in accordance with applicable standard operating procedures. Note: The follow-up visits at 30 days, 1–5 years, 7 years, and 10 years must be conducted in-person.	
			11.10.7 Procedure for Determining…	• Failure to complete 2 consecutive visits (or telephone follow-up as indicated in Table 11.1 1) without due cause…	

Table 26.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
			11.11 Study Completion	All subjects who receive a test device will be evaluated at 30 days and then annually up to 10 years post index procedure. Visits in the first 5 years and at 7 and 10 years are office or in-person visits. Evaluations may be conducted by telephone at 6, 8 and 9 years. A subject's participation in the study will be considered complete after the 10-year visit.	
			12.2.3 Reporting Events	For time based clinical events, the cut-off for events for 30-day endpoints will be 30 days, for 1-year endpoints it will be 365 days, and for 2-10 year endpoints it will be 365 days times the number of years.	
			20.1 Reportable Events…	Based on the VARC… • Bleeding events: Life-threatening… (through 5 years) • Vascular complications: major (including annular rupture; through 5 years)	Updated for clarity
			27.1.4 Protocol Version D to Version E	Table 27.1-4 lists changes between protocol versions D and E. Table 27.1-4: Table of Changes for REPRISE IV Protocol Version E (Compared to REPRISE IV Protocol Version D)	
F	29-Apr-2020	90702637 Rev/Ver AL	Entire Document	Document transferred from template version AG to template version AL.	Updated protocol template
			Page 1	Added National Clinical Trial Identification Number: NCT03618095	
			Page 2	Current Version: 29-Apr-2020 Updated Table of Revision History	
			Synopsis, Planned Number of Subjects…	Subjects will be enrolled at up to ~~50~~65 centers… There will be up to ~~896~~926 subjects… Roll-In: Up to ~~100~~130	Addition of up to 15 centers
			Synopsis, Adjunctive Pharmacologic Therapy	Anti-Platelet Therapy Per society guidelines[b], antiplatelet therapy with aspirin and/or a $P2Y_{12}$ inhibitor… medications. Study subjects must receive some antiplatelet therapy (aspirin and/or a P2Y12 inhibitor) for at least 1 month following valve implant. A loading dose of the same antiplatelet medication (aspirin and/or a $P2Y_{12}$ inhibitor) is required for subjects who have not been on the antiplatelet therapy for ≥72 hours at the time of the index procedure (see below for recommended doses).	Reflects current standard of care

Table 26.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				Note 5: It is recommended that subjects be treated with both aspirin and a $P2Y_{12}$ inhibitor for at least 1 month after valve implantation. Aspirin Dose ~~A~~ The recommended loading dose of aspirin ~~(recommended dose of~~ is 75–325 mg~~) is required~~ for subjects who… Subjects…loading dose of aspirin. After the valve implant procedure, ~~aspirin (~~the recommended dose of aspirin is ≥75 mg daily~~) must be~~ given for at least 1 month… $P2Y_{12}$ Inhibitor Dose (clopidogrel recommended) ~~A~~ The recommended loading dose of a $P2Y_{12}$ inhibitor is ~~(recommended dose of~~ ≥300 mg ~~for~~ clopidogrel, 60 mg ~~for~~ prasugrel, or 180 mg ~~for~~ ticagrelor~~) is required~~ for subjects who have not... Subjects who have been taking a $P2Y_{12}$ inhibitor daily for ≥72 hours at the time of the index procedure do not require a loading dose of the $P2Y_{12}$ inhibitor. After the valve implant procedure, the recommended ~~a~~ $P2Y_{12}$ inhibitor dosing is per local standard of care ~~is required~~ for at least 1 month… **Note ~~5~~6:** If a subject… or aspirin is ~~required~~ recommended prior to… (but both aspirin and a P2Y12 inhibitor are not ~~required~~ recommended). After the implant procedure, the subject ~~must~~ should be treated...	
			Synopsis, Sample Size Parameters	† Estimated pooled rate from the fixed~~/random~~ effect~~s~~ model based on the ~~ITT~~ TAVR arm data…	Updated for clarity
			Section 6/Section 7	Sections 6 and 7 merged into Section 6 Study Objectives and Endpoints addition of Sections 6.1 and 6.2	Updated protocol template
			Section 7.1 Scale and Duration	…There will be a roll-in phase (up to ~~100~~130 subjects) for… Updated Figure 7.1-1 REPRISE IV Study Design	Addition of up to 15 centers (additional 30 Roll-In subjects)
			Section 7.3 Justification of the…	There will be up to ~~896~~926 subjects… In order to … study subjects to risk, up to ~~100~~130 subjects… Up to ~~50~~65 centers… …antiplatelet therapy with aspirin and/or a P2Y12 inhibitor is recommended after TAVR…	Addition of up to 15 centers Reflect current standard of care

Table 26.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
			Sections 7 through 11	Sections 8 through 12 updated to Sections 7 through 11; some subsections moved to accommodate new protocol template; for example: 11.10.7 moved to 9.4; 11.10.8 moved to 9.2	Updated protocol template
			Section 9.2 Discontinuation of Study Intervention	Section 11.10.8 Explant Procedure moved to Section 9.2.	
			Section 9.4 Lost to Follow-Up	Section 11.10.7 Procedure for Determining when a subject is Lost to Follow-up moved to Section 9.4.	
			Section 10.1 Data Collection	Added paragraph: This section indicates the data needed to fulfill the objectives of this clinical study. Boston Scientific Corporation considers data collected from clinical trial subjects to be personal data (see definitions of different data categories in Table 25.2 1) and compliance with privacy and data protection laws and regulations (for example, the General Data Protection Regulation [GDPR]) to be critically important. Data collection for this clinical study has been carefully considered to comply with data privacy laws.	
			New Section 10.2.1 Strategies for Recruitment and Retention	New section; select information moved from Section 9.1 Study Population and Eligibility to new Section 10.2.1 The REPRISE IV study will include subjects presenting with documented severe native aortic valve stenosis who are indicated for TAVR (see Section 8). It is estimated that nearly 5% of elderly ≥75 years of age have aortic stenosis and its prevalence is expected to increase due to an aging population2,3. Because aortic stenosis most commonly occurs in the very elderly, women are well represented in TAVR trials. Traditionally underrepresented populations (elderly and women) are expected to be included in the subject population as allowed by governing law/national regulation; as the very elderly will represent the majority of subjects enrolled in the trial, efforts to maximize retention are by definition targeted to traditionally under-represented groups. The inclusion and exclusion criteria are not expected to have a negative effect on recruitment or retention of said populations. In the United States, the subjects eligible for inclusion in this study are likely to be Medicare	

Table 26.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				patients due to their expected age and the results of this study are likely to be highly generalizable to a Medicare population. All efforts will be made to minimize attrition in REPRISE IV (see Section 9.4). Investigators are encouraged to enroll subjects who are willing to comply with the follow-up requirements of the study. If a visit is missed, the center should attempt to contact the subject to reschedule the missed visit and counsel the subject on the importance of maintaining the assigned visit schedule.	
			Section 10.4 Screening…	▪ Maximum grip… using a ~~Jamar~~ hand-held…	Updated for clarity
			Section 10.6 Pre-procedure Medications	▪ Antiplatelet Therapy: Per society guidelines[10,121] antiplatelet therapy is recommended to reduce the risk of thrombotic or thromboembolic complications if there are no contraindications to these medications. Study subjects must receive some antiplatelet therapy (aspirin and/or a P2Y12 inhibitor) for at least 1 month following valve implant. A loading dose of the same antiplatelet medication (aspirin and/or a P2Y12 inhibitor) is required for subjects who have not been on the antiplatelet therapy for ≥72 hours at the time of the index procedure (see below for recommended doses). Aspirin Dose ~~A~~ The recommended loading dose of aspirin is ~~(recommended dose of~~ 75-325 mg~~) is required~~ for subjects… dose of aspirin. P2Y12 Inhibitor Dose (Clopidogrel Recommended) ~~A~~ The recommended loading dose of a $P2Y_{12}$ inhibitor is ≥300 mg clopidogrel, ~~at a dose of ≥300 mg is recommended; for other P2Y12 inhibitors recommended doses are~~ 60 mg ~~for~~ prasugrel, ~~and~~ or 180 mg ticagrelor~~) is required~~ for… Subjects who have been taking a $P2Y_{12}$ inhibitor daily for ≥72 hours at the time of the index procedure do not require a loading dose of the $P2Y_{12}$ inhibitor. ***Note:*** If a subject is treated with anticoagulation, either a $P2Y_{12}$ inhibitor or aspirin is ~~required~~ recommended prior to the implant	Reflect current standard of care

Table 26.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				procedure (but both aspirin and a P2Y$_{12}$ inhibitor are not ~~required~~ recommended).	
			Section 10.7 Index Procedure	~~In the United States, CMS coverage… index procedure.~~ Moved Note 1 and Note 2 as shown below. The preparation of the subject… approach to treat the subject. Note 1: Additional… procedure. Note 2: The subject… Form. The large Lotus Introducer… 8) A final post-deployment… ~~(including rotational angiography of the valve frame)~~ must…	Change to CMS requirements Updated for clarity
			Section 10.8 Post Index Procedure	• Per society guidelines… Study subjects must receive some antiplatelet therapy (aspirin and/or a P2Y$_{12}$ inhibitor) for at least 1 month following valve implant. It is recommended that subjects ~~must~~ be treated with aspirin and a P2Y$_{12}$ inhibitor for at least 1 month ~~following valve implantation~~. Extended… ○ After the valve implant procedure, aspirin (recommended dose of ≥75 mg daily) ~~must~~ should be given… ○ After the valve implant procedure, a P2Y$_{12}$ inhibitor is recommended ~~required~~ for at least 1 month… ○ If a subject is treated with chronic anticoagulation, either a P2Y$_{12}$ inhibitor or aspirin is ~~required~~ recommended after the implant procedure in addition to the anticoagulant therapy (but both aspirin and a P2Y$_{12}$ inhibitor are not ~~required~~ recommended). The subject ~~must~~ should be treated…	Reflect current standard of care
			Section 10.10 Follow-up	***Note 1***: The follow-up visits at 30 days, 1–5 years, 7 years, and 10 years must be conducted in-person. If an in-person assessment cannot be performed, follow-up by telephone should be attempted. Subject or subject's physician should provide rationale for why the in-person assessment cannot be performed.	FDA request to extend trial to 10 years.
			Section 11.1.1.2 Sample Size Parameters…	* Estimated pooled rate from the fixed~~/random~~ effect~~s~~ model based on the ~~ITT~~ TAVR arm data from…	Updated for clarity

Table 26.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
			Section 11.2.2 Control of Systematic…	…These include an echocardiography core laboratory, a CT and procedural ~~rotational X-ray~~ angiography core laboratory to assess all CT and procedural angiography ~~rotational X-ray~~ data using…	
			New Section 12 Health Economics…	New section; select information moved from Sections 11.10.1, 11.10.2, and 11.10.3 moved to new Section 12	Updated protocol template
			Sections 14 through 25	Section numbers 15 through 26 updated to Sections 14 through 25; Section 27 (Appendices) removed as all protocol changes are captured in the Revision History Table	Updated protocol template New information in the literature
			Section 16.3 Institutional Review Board/Human Research Ethics Committee	Section 14 Amendments removed; information on amendments found in Section 16.3 …provided to the subject. If a protocol revision is necessary which affects the rights, safety or welfare of the subjects or scientific integrity of the data, an amendment is required. Any amendment…	Updated protocol template
			Section 16.4.1 Role of Boston Scientific…	Section 17 renumbered to Section 16 per updated protocol template. Boston Scientific… engineers and specialists) who… **Boston Scientific personnel will not do the following.** • Enter… systems or on paper case report forms.	Updated for clarity
			Section 16.4.2 Training with the Investigational Device	• Patient… the ~~Directions~~ Instructions for Use (~~DFU~~IFU) and… • Implantation… from the ~~DFU~~IFU. Training… • Proctoring: The investigator… proctored by an individual experienced with the LOTUS *Edge* valve and TAVR ~~physician~~ on a minimum…	Updated for clarity Updated to allow non-physician proctors
			Section 18.1 Anticipated…	Moved text about risks into new Table 18.1-1 Risks Associated with Transcatheter Aortic Valve Replacement	Updated protocol template
			Section 18.1.1 Hypoattenuated Leaflet Thickening/Reduced	Add new section 18.1.1 Hypoattenuated leaflet thickening (HALT) and reduced leaflet motion (RLM) suggestive of subclinical leaflet thrombosis, as detected by high-	Updated for clarity

Table 26.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
			Leaflet Motion/Leaflet Thrombosis	resolution CT, has been reported with bioprosthetic TAVR and SAVR valves[40,109,128,129]. It is less common among subjects receiving anticoagulant therapy and, in some cases, has been shown to resolve with such treatment[40,109,110,128-131]. Clinical signs of HALT and RLM include elevation of transvalvular gradients (as determined by echocardiography), central or peripheral thromboembolic events, and unexpected recurrence of heart failure. Computed tomography imaging is recommended to appropriately assess subjects with echocardiographic and/or clinical suspicion of leaflet thrombosis. Additional anticoagulant therapy may be indicated based on symptoms or signs and subject bleeding risk[40,109,110,128-131]. The subset of subjects undergoing 4D CT scans at 30 days and 1 year will be exposed to an additional radiation dose of about 20 milliSieverts (mSv), which is equivalent to about 10 years' worth of natural background radiation. The contrast dye used during the image acquisition can cause medical problems such as allergic reactions and increase the risk of worsening kidney function or failure.	
			Section 18.3 Risks…	Risks… listed above in Table 18.1-1.	New Table 18.1-1
			Section 19.3 Relationship to…	In Table 19.3-1 removed the row for "Unlikely Related."	Updated regulations and definitions
			Section 25.2	New definitions for Data Categories and General Data Protection Regulation; remove definition for Structural Valve Deterioration; added definitions for Hypoattenuated Leaflet Thickening and Reduced Leaflet Motion	
			New Section 26 Revision History	Added new Section 26 Revision History; merged the revision history tables into 1 table (called Table 26.1-1) per the new protocol template. New updates in the table show changes from Protocol Version D to Version E to Version F	Updated for clarity and per the new protocol template