REPRISE II: REpositionable Percutaneous Replacement of Stenotic Aortic Valve through Implantation of Lotus™ Valve System – Evaluation of Safety and Performance

CLINICAL PROTOCOL

Protocol Number: TP3687

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Revision History

Revision Number	Release Date	Reason for Change
AB	07-Aug-2012	See Table 27.1-1
AC	13-Aug-2012	See Table 27.1-2
AD	05-Sept-2012	See Table 27.1-3
AE	20-Dec-2012	See Table 27.1-4
AF	12-Mar-2013	See Table 27.1-5

2. Protocol Synopsis

REPRISE II: Repositionable Percutaneous Replacement of Stenotic Aortic Valve through Implantation of Lotus™ Valve System – Evaluation of Safety and Performance	
Objective(s)	To evaluate the safety and performance of the Lotus™ Valve System for transcatheter aortic valve replacement (TAVR) in symptomatic subjects with severe calcific aortic stenosis who are considered high risk for surgical valve replacement.
Intended Use	The Lotus Valve System is intended to improve aortic valve function for symptomatic subjects with severe calcific aortic stenosis (aortic valve area [AVA] of <1.0 cm^2 or index of <0.6 cm^2/m^2) who are at high risk for standard surgical valve replacement.
Test Device	The Lotus Valve System consisting of two main components: - a bioprosthetic bovine pericardial aortic valve - a delivery system.
Device Sizes	The sizes of the Lotus Valve used in this study will include the 23 mm diameter size suitable for subjects with aortic annulus diameter between ≥20 mm and ≤23 mm, and the 27 mm diameter size suitable for aortic annulus diameter between ≥23 mm and ≤27 mm. ***Note:*** The commercially approved Lotus Introducer Set will be used as an accessory to the Lotus Valve System during the procedure. The Lotus Introducer provided for use with the 23 mm valve will be suitable for use in subjects with femoral artery lumen diameter ≥6.0 mm, and the Lotus Introducer provided for use with the 27 mm valve will be suitable for use in subjects with femoral artery lumen diameter ≥6.5 mm.
Comparator	For the device performance primary endpoint, a performance goal (PG) based on the 30-day mean aortic valve pressure gradient derived from published literature will be used as the comparator for analysis. For the primary safety endpoint, a performance goal (PG) based on 30-day all-cause mortality data derived from published literature will be used as the comparator for analysis.
Study Design	The REPRISE II clinical study is a prospective, single-arm, multicenter study designed to evaluate the safety and performance of the Lotus Valve System for TAVR in symptomatic subjects who have severe calcific aortic valve stenosis and who are at high risk for surgical aortic valve replacement

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	(SAVR). A total of up to 120 subjects will be enrolled in the main study at up to 15 centers. Subsequently, up to 130 additional subjects will be enrolled at up to 21 centers in the extended trial cohort. The statistical hypotheses for the main trial cohort and the combined (main + extended) cohorts are described below. The REPRISE II study will be conducted in accordance with the International Standard ISO 14155: 2011; ethical principles that have their origins in the Declaration of Helsinki; the relevant parts of the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practices (GCP); and pertinent individual country/state/local laws and regulations.
Planned Number of Subjects	A total enrollment of up to 120 subjects is planned for the main study. Subsequently, up to 130 additional subjects (250 subjects in total) will be enrolled in the extended trial cohort.
Planned Number of Centers / Countries	The main study will enroll subjects at up to 15 centers in these possible countries: Australia, France, Germany and United Kingdom. The extended trial cohort will enroll subjects at up to 21 centers in Australia and European countries.
Primary Endpoints	Primary Device Performance Endpoint: Mean aortic valve pressure gradient at 30 days post implant procedure as measured by echocardiography and assessed by an independent core laboratory Primary Safety Endpoint: All-cause mortality at 30 days post implant procedure
Secondary Endpoints	• Effective orifice area at 30 days as measured by echocardiography and assessed by an independent core laboratory • Device Performance endpoints peri- and post-procedure: o Successful vascular access, delivery and deployment of the Lotus Valve System, and successful retrieval of the delivery system o Successful repositioning of the Lotus Valve System if repositioning is attempted o Successful retrieval of the Lotus Valve System if retrieval is attempted

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	○ Grade of aortic valve regurgitation: paravalvular, central and combined • Device Success based on the Valve Academic Research Consortium definitions (VARC)[a, b] ***Note:*** 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. a: Kappetein AP, et al. *J Am Coll Cardiol*. 2012;60:1438 b: Leon MB, et al. *J Am Coll Cardiol.* 2011;57:253
Additional Measurements	Additional measurements based on the VARC[a,b] endpoints and definitions (see Table 26.2-1 for definitions) will be collected peri- and post-procedure, at discharge or 7 days post-procedure (whichever comes first), 30 days, 3 months, 6 months, and 1, 2, 3, 4, and 5 years post index procedure, unless otherwise specified below. • Safety endpoints adjudicated by an independent Clinical Events Committee (CEC): ○ Mortality: all-cause, cardiovascular, and non-cardiovascular ○ Stroke: disabling and non-disabling ○ Composite of all-cause mortality and disabling stroke ○ Myocardial infarction (MI): periprocedural (≤72 hours post index procedure) and spontaneous (>72 hours post index procedure) ○ Bleeding: life-threatening (or disabling) and major ○ Acute kidney injury (≤7 days post index procedure): based on the AKIN System Stage 3 (including renal replacement therapy) or Stage 2 ○ Major vascular complication ○ Repeat procedure for valve-related dysfunction (surgical or interventional therapy) ○ Hospitalization for valve-related symptoms or worsening congestive heart failure (NYHA class III or IV) ○ New permanent pacemaker implantation resulting from new or worsened conduction disturbances (including new left bundle branch block [LBBB] and third degree atrioventricular block) ○ New onset of atrial fibrillation or atrial flutter

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	○ Coronary obstruction (periprocedural) ○ Ventricular septal perforation (periprocedural) ○ Mitral apparatus damage (periprocedural) ○ Cardiac tamponade (periprocedural) ○ Prosthetic aortic valve malapposition, including valve migration, valve embolization, ectopic valve deployment, or transcatheter aortic valve (TAV)-in-TAV deployment ○ Prosthetic aortic valve thrombosis ○ Prosthetic aortic valve endocarditis • Prosthetic aortic valve performance as measured by transthoracic echocardiography (TTE) and assessed by an independent core laboratory, including effective orifice area, mean and peak aortic gradients, peak aortic velocity, and grade of aortic regurgitation • Functional status as evaluated by the following: ○ 5-m gait speed test (at 1 year compared to baseline) ○ New York Heart Association (NYHA) classification • Neurological status as determined by the following: ○ National Institutes of Health Stroke Scale (NIHSS) at discharge and 1 year ○ Modified Rankin Scale (mRS) • Health status as evaluated by SF-12 and EQ-5D Quality of Life questionnaires at baseline; 1 and 6 months; and 1, 3, and 5 years ***Note 1:*** The VARC safety composite at 30 days will be reported; this includes all-cause mortality, all stroke, life-threatening bleeding, acute kidney injury Stage 2 or 3 (including renal replacement therapy), coronary artery obstruction requiring intervention, , major vascular complication, and repeat procedure for valve-related dysfunction (surgical or interventional therapy). ***Note 2:*** The VARC efficacy composite at 1 year will be reported. This includes all-cause mortality (after 30 days); all stroke; requiring hospitalization for valve-related symptoms or worsening congestive heart failure (NYHA class III or IV); and prosthetic heart valve dysfunction (mean aortic valve gradient ≥20 mm Hg, effective orifice area ≤0.9-1.1 cm^2,and/or Doppler velocity index (DVI) <0.35 AND/OR moderate or severe prosthetic valve aortic regurgitation [per VARC definition]). ***Note 3:*** Time-related valve safety composite will be reported. This includes

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	structural valve deterioration (valve-related dysfunction requiring repeat procedure [TAVR or SAVR]), prosthetic valve endocarditis, prosthetic valve thrombosis, thromboembolic events (e.g., stroke), and VARC bleeding (unless clearly unrelated to valve therapy based on investigator assessment). ***Note 4:*** A total enrollment of up to 120 subjects is planned for the main study. Subsequently, up to 130 additional subjects will be enrolled for the extended trial cohort. In the main study, for subjects diagnosed with a neurological event (e.g., stroke, transient ischemic attack), a neurological physical exam, NIHSS assessment, and mRS must be performed after the event; mRS must also be administered at 90 days post-neurological event. In the extended trial cohort, for subjects diagnosed with a neurological event, NIHSS assessment and mRS must be performed after the event; mRS must also be administered at 90 days post-neurological event; the neurological physical exam is not required in the extended trial cohort. a: Kappetein AP, et al. *J Am Coll Cardiol*. 2012;60:1438 b: Leon MB, et al. *J Am Coll Cardiol.* 2011;57:253
Follow-up Schedule	All subjects implanted with the Lotus Valve will be assessed at baseline, peri- and post-procedure, at discharge or 7 days post-procedure (whichever comes first), 30 days, 3 months, 6 months, and then annually for up to 5 years post-procedure. Subjects who are not implanted with the Lotus Valve at the time of the procedure will be followed for safety through 30 days.
Study Duration	Subjects implanted with the Lotus Valve will be followed for up to 5 years after the procedure.
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. **Anti-Platelet Therapy** Subjects must be treated with aspirin and a thienopyridine prior to implantation of the Lotus Valve and for at least 1 month following valve implantation. Per society guidelines[c], antiplatelet therapy with aspirin and clopidogrel[d] is recommended after TAVR to decrease the risk of thrombotic or thromboembolic complications if there are no

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	contraindications to these medications. Aspirin A loading dose of aspirin (recommended dose of 75–325 mg) is required for subjects who have not been taking aspirin for ≥72 hours at the time of the index procedure. The loading dose must be administered prior to the implant procedure or immediately after. Subjects who have been taking aspirin daily for ≥72 hours at the time of the index procedure do not require a loading dose. After the Lotus Valve implant procedure, aspirin (recommended dose of ≥75 mg daily) must be given for at least 1 month. It is recommended that daily aspirin be given indefinitely thereafter as per local standard of care. Aspirin doses may be adjusted to the closest approximation based on local tablet formulation availability. Clopidogrel[d] A loading dose of clopidogrel (recommended dose of ≥300 mg) is required for subjects who have not been taking clopidogrel for ≥72 hours at the time of the index procedure. The loading dose must be administered prior to the implant procedure or immediately after. After the Lotus valve implant procedure, clopidogrel (recommended dose of 75 mg daily) is required for at least 1 month. ***Note 1*:** If the study-specific dosages and durations for antiplatelet medications conflict with country-specific labeling for the medications, the country-specific labeling should take precedence. ***Note 2*:** If a subject requires chronic anticoagulation (e.g., warfarin, dabigatran, etc.), either clopidogrel[d] or aspirin is required prior to and after implant procedure in addition to the anticoagulant therapy (but both aspirin and clopidogrel are not required). c: Holmes, D. R., et al. *J Am Coll Cardiol*. 2012;59:1200. d: An alternative P2Y12 inhibitor may be prescribed if subject is allergic to or intolerant of clopidogrel.
Inclusion Criteria	IC1. Subject is ≥70 years of age IC2. Subject has documented calcific native aortic valve stenosis with an initial aortic valve area (AVA) of <1.0 cm^2 (or AVA index of <0.6 cm^2/m^2) and either a mean pressure gradient >40 mm Hg or a jet velocity >4 m/s, as measured by echocardiography IC3. Subject has a documented aortic annulus size between ≥20 and ≤27 mm based on pre-procedure diagnostic imaging

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	IC4. Symptomatic aortic valve stenosis with NYHA Functional Class ≥ II IC5. Subject is considered high risk for surgical valve replacement based on at least one of the following: a. Society of Thoracic Surgeons (STS) score ≥8%, AND/OR b. Agreement by the heart team (which must include an in-person evaluation by an experienced cardiac surgeon) that subject is at high operative risk of serious morbidity or mortality with surgical valve replacement IC6. Heart team (which must include an experienced cardiac surgeon) assessment that the subject is likely to benefit from valve replacement. IC7. Subject (or legal representative) understands 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.
Exclusion Criteria	EC1. Subject has a congenital unicuspid or bicuspid aortic valve. EC2. Subject with an acute myocardial infarction within 30 days of 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 within the past 6 months, or has any permanent neurologic defect prior to study enrollment. EC4. Subject is on dialysis or has serum creatinine level >3.0 mg/dL or 265 µmol/L. EC5. Subject has a pre-existing prosthetic heart valve (aortic or mitral) or a prosthetic ring in any position. EC6. Subject has ≥3+ mitral regurgitation, ≥3+ aortic regurgitation or ≥3+ tricuspid regurgitation (i.e., subject cannot have more than moderate mitral, aortic or tricuspid regurgitation). EC7. Subject has a need for emergency surgery for any reason. EC8. Subject has a history of endocarditis within 12 months of index procedure or evidence of an active systemic infection or sepsis. EC9. Subject has echocardiographic evidence of intra-cardiac mass, thrombus or vegetation.

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	EC10. Subject has Hgb <9 g/dL, platelet count <50,000 cells/mm^3 or >700,000 cells/mm^3, or white blood cell count <1,000 cells/mm^3. EC11. Subject requires chronic anticoagulation therapy (e.g., warfarin, dabigatran, etc.) and cannot tolerate concomitant therapy with either aspirin or clopidogrel[d]. ***Note:*** Subjects who require chronic anticoagulation must be able to be treated additionally with either aspirin or clopidogrel[d]. EC12. Subject has active peptic ulcer disease or gastrointestinal bleed within the past 3 months, other bleeding diathesis or coagulopathy or will refuse transfusions. EC13. Subject has known hypersensitivity to contrast agents that cannot be adequately pre-medicated, or has known hypersensitivity to aspirin, all thienopyridines, heparin, nickel, tantalum, titanium, or polyurethanes. EC14. Subject has a life expectancy of less than 12 months due to non-cardiac, co-morbid 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 procedure (including balloon aortic valvuloplasty) within 30 days prior to the index procedure (except for pacemaker implantation which is allowed). EC17. Subject has untreated coronary artery disease, which in the opinion of the treating physician is clinically significant and requires revascularization. EC18. Subject has documented left ventricular ejection fraction <30%. EC19. Subject is in cardiogenic shock or has hemodynamic instability requiring inotropic support or mechanical support devices. EC20. Subject has severe peripheral vascular disease (including aneurysm defined as maximal luminal diameter >5 cm or with documented presence of thrombus, marked tortuosity, narrowing of the abdominal aorta, severe unfolding of the thoracic aorta or thick [>5 mm], protruding or ulcerated atheroma in the aortic arch) or symptomatic carotid or vertebral disease. EC21. Femoral artery lumen of <6.0 mm for subjects requiring 23 mm valve size or <6.5 mm for subjects requiring 27 mm valve size, or severe iliofemoral tortuosity or calcification that would prevent safe placement of the introducer sheath.

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	EC22. Current problems with substance abuse (e.g., alcohol, etc.). 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. d: An alternative P2Y12 inhibitor may be prescribed if subject is allergic to or intolerant of clopidogrel.
Statistical Methods – Main Trial Cohort (N=120)	
Primary Statistical Hypothesis	Mean aortic valve pressure gradient at 30 days post implant procedure is less than the performance goal (PG) of 18 mmHg
Statistical Test Method	A one-sample *t*-test will be used to test the one-sided hypothesis: H_0: $Gradient_{30D} \geq PG$ H_1: $Gradient_{30D} < PG$ where $Gradient_{30D}$ is the 30-day mean aortic valve pressure gradient for the Lotus Valve and PG is 18 mmHg.
Sample Size Parameters	• Expected 30-day mean pressure gradient from Lotus Valve ≤15 mmHg • Expected standard deviation = 7 mmHg • PG = 18 mmHg • Test significance level (α) = 0.025 (1-sided) • Power ≥ 80% • Evaluable number of subjects = Minimum of 49 subjects • Expected rate of attrition = 15% (9 subjects) • Planned enrollment of up to 120 subjects • Two planned interim analyses will be performed on the first 40 and 60 subjects enrolled based on the primary endpoint at 30 days post-implant procedure • A final analysis will be performed on all subjects enrolled in the main trial cohort (120 subjects) • The primary analysis population for the primary endpoint will be the

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	subject population implanted with the Lotus Valve. ***Note 1*:** The expected 30-day mean aortic valve pressure gradient is assumed to be ≤15 mmHg based on a literature review of studies evaluating the Medtronic CoreValve System and the Edwards Lifesciences SAPIEN Transcatheter Heart Valve System. ***Note 2*:** The alpha-level for the interim and final analyses of the main trial cohort is adjusted using the Pocock alpha spending function (see Success Criteria below).
Success Criteria	Two interim analyses will be conducted on the first 40 and 60 subjects and a final analysis will be conducted on the fully enrolled main trial cohort (N=120). The Pocock alpha spending function is used to adjust the alpha-level for each analysis: 0.01123, 0.00792, and 0.01305, respectively. If the *P* value from the one-sample *t*-test is <alpha, the Lotus Valve will be concluded to have a 30-day mean aortic valve pressure gradient <18 mm Hg. This corresponds to the one-sided upper (1-alpha)% confidence bound of the observed 30-day mean aortic valve pressure gradient being <18 mmHg.
Statistical Methods – Combined Main and Extended Trial Cohort (N=250)	
Primary Statistical Hypothesis	All-cause mortality at 30 days post implant procedure is less than the PG of 16 % (expected rate of 9.8% + testing margin of 6.2%)
Statistical Test Method	A one-sample z-test will be used to test the one-sided hypothesis: H_0: $Mortality_{30D} \geq PG$ H_1: $Mortality_{30D} < PG$ where $Mortality_{30D}$ is the 30-day all-cause mortality rate for the Lotus Valve and PG is 16%.

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Sample Size Parameters	• Expected 30-day all-cause mortality rate = 9.8% • Performance goal (PG) = 16 % (expected rate of 9.8% + testing margin of 6.2%) • Test significance level (α) = 0.025 (1-sided) • Power ($1 - \beta$) = 80% • Expected rate of attrition = 2% • Planned enrollment of up to 250 subjects (main trial cohort enrollment of 120 subjects plus extended trial cohort enrollment of 130 subjects) ***Note***: The expected 30-day all-cause mortality rate is assumed to be 9.8% based on a literature review of studies evaluating the Medtronic CoreValve System and the Edwards Lifesciences SAPIEN Transcatheter Heart Valve System.
Success Criteria	If the *P* value from the one-sample *z*-test is <0.025, it will be concluded that the primary safety endpoint for the Lotus Valve is less than the PG. This corresponds to the one-sided upper 97.5% confidence bound of the observed 30 day mortality rate being <16 %.

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™ Valve System, a transfemoral aortic valve replacement device designed and manufactured by Boston Scientific Structural Heart a Division of Boston Scientific Corporation. The Lotus Valve System consists of a pre-loaded, stent-mounted tissue valve prosthesis and catheter delivery system designed to enable predictable and precise placement of the valve during transcatheter aortic valve replacement (TAVR). Early leaflet function during valve deployment and the presence of a radiopaque tantalum marker on the braided frame facilitates optimal initial positioning of the valve. If needed, the valve may be un-locked after being locked and partially or fully 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 polyurethane outer seal (Adaptive™ Seal) designed to minimize paravalvular leakage. Additional device information can be found in Section 5.

4.1. *Justification for the Use of the Investigational Device in Human Subjects*

4.1.1. Treatments for Aortic Stenosis

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

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

Transcatheter aortic valve replacement has recently emerged as an alternative to the surgical approach in the treatment of severe AS in subjects who are not suitable candidates for open-heart surgery[7]. This technology is generally restricted to subjects considered at prohibitive or high surgical risk. Evidence of the safety of the procedure using either a balloon expandable or a self-expanding bioprosthetic heart valve has rapidly accumulated through observational studies[8-15], device-specific registries[16-22], national registries[23-26], and randomized controlled

trials[27,28]. Through 2-year follow-up in the PARTNER US IDE trial there have been significant reductions in mortality and repeat hospitalization rates compared to standard medical therapy in subjects unsuitable for SAVR[29], and similar mortality rates compared to surgical valve replacement in high-surgical-risk subjects[30]. An expert consensus document on TAVR was recently published[31].

Table 4.1-1 summarizes the peri-operative event rates through 30 days post-procedure from several TAVR studies that enrolled similar subjects as those planned for this study, as well as the results from the inoperable (Cohort B) and high risk (Cohort A) subjects with severe aortic stenosis enrolled in PARTNER [27,28]. A more detailed summary of the available literature is presented in the Investigator Brochure.

Table 4.1-1: Events from Peri-Operative to 30 Days (Transfemoral Approach)

Study	Device/N	Death	MI	Major Stroke	Bleeding	Acute Kidney Injury	Vascular Compli-cations
Webb, et al. 2006[32]	EW/18	11%	0%	0%	N/A	N/A	N/A
Webb, et al. 2007[33]	EW/50	12%	2%	4%	N/A	N/A	N/A
Webb, et al. 2009[8]	EW/113[a]	8%	N/A	5.3%	11.6%	4.4%	8%
Osten, et al. 2010[9]	EW/16	6%	0%	6%	13%	0%	13%
Rodés-Cabau, et al. 2010[17]	EW/168[a]	9.5%	0.6%	3.0%	N/A	N/A	N/A
Thomas, et al. 2010[18]	EW/463[a]	6.3%	N/A	2.4%	9.9%	1.3%	22.9%
Leon, et al. 2010[27]	EW/267[b]	5%	0%	5%	16.8%	1.1%	16.2%[c] 30.7%
Smith, et al. 2011[28]	EW/244[a,d]	3.4%	0%	3.8%	9.3%	2.9%	14%[c] 22.7%
Lefèvre, et al. 2011[20]	EW/55	8.2%	3.3%	3.3%	23.5%	0%	28.4%
Grube, et al. 2006[34]	CV/25	20%	0%	4%	N/A	N/A	N/A
Grube, et al. 2007[35]	CV/86	12%	1%	10%	N/A	N/A	N/A
Piazza, et al. 2008[16]	CV/646	8%	0.6%	1.9%[e]	N/A	N/A	1.2%
Baan, et al. 2010[36]	CV/30	20%	0%	0%	N/A	N/A	N/A
Munoz-Garcia, et al. 2012[22]	CV/133[f]	4.5%	0.8%	1.5%	N/A	N/A	2.2%[c]
Bullesfeld, et al. 2011[12]	CV/72[b,d,g]	18.1%	5.6%	8.3%[e]	N/A	N/A	N/A
Buchanan, et al.	CV,	4.7%	1.3%	1.0%	33.1%	10.2%[h]	15.7%[c]

Table 4.1-1: Events from Peri-Operative to 30 Days (Transfemoral Approach)

Study	Device/N	Death	MI	Major Stroke	Bleeding	Acute Kidney Injury	Vascular Compli-cations
2011[11]	EW/305						
Moat, et al. 2011[25]	CV, EW/599	5.5%	1.0%	4.0%[i]	N/A	N/A	6.2%
Stohr, et al. 2011[10]	CV/73[a] EW/82[j]	12%[k]	N/A	1.0%	N/A	4.0%	N/A
Zahn, et al. 2011[24]	CV, EW/697[l]	12.4%	0.3%	2.8%[e]	N/A	N/A	17.1%[m]
Bosmans, et al. 2011[37]	CV/133[a] EW/99[a]	8% (CV); 6% (EW)	N/A	5%[e,n]	N/A	6%[n,o]	N/A
Tamburino, et al. 2012[13]	CV, EW/218[p]	6.9%	0.0%	2.3%	5.5%	N/A	N/A
Gilard, et al. 2012[26]	CV, EW/2361[a]	8.5%	0.8%	2.2%	1.2%[q]	N/A	5.5%[c]

a: Transfemoral approach population only
b: Inoperable subjects
c: Major
d: High risk subjects
e: All stroke
f: Femoral access in 90.9% of cases
g: Femoral access in 98% of cases
h: Stage 3
i: In hospital
j: Apical access only
k: Includes apical and transfemoral
l: 92.4% transfemoral and 3.2% subclavian; 84% of all procedures were CV
m: Groin problem with need of transfusion
n: All subjects
o: Dialysis
p: Femoral access in 97.2% of cases
q: Life-threatening bleeding
Abbreviations: CV=CoreValve; EW=Edwards; MI=myocardial infarction; N/A=not available

4.1.2. REPRISE I Study

The aforementioned results notwithstanding, TAVR with early generation devices has been associated with increased stroke risk versus surgical valve replacement[28,30]. Cerebrovascular accidents and vascular complications associated with TAVR have been significant predictors of mortality[38,39]. The paravalvular regurgitation more commonly seen with TAVR compared to surgery has also been accompanied by higher early and late mortality[21,30,40]. While careful subject selection may serve to mitigate these risks[41-43], device design improvements such as seen with the Lotus Valve System (Section 5.1) may enable more precise placement,

minimize or eliminate paravalvular regurgitation, and obviate the need for valve-in-valve repeat intervention.

The prospective, single arm, multicenter REPRISE I (REpositionable Percutaneous Replacement of Stenotic Aortic Valve through Implantation of Lotus™ Valve SystEm) feasibility study (N=11) assessed the acute safety and performance of the Lotus Valve System in symptomatic subjects with calcified stenotic aortic valves who were considered high risk for surgical valve replacement. The primary endpoint was clinical procedural success, defined as successful implantation of a Lotus Valve (per the Valve Academic Research Consortium [VARC] definitions[44]) without in-hospital major adverse cardiovascular and cerebrovascular events (MACCE, defined as all-cause mortality, periprocedural myocardial infarction ≤72 hours after the index procedure, major stroke, urgent/emergent conversion to surgery or repeat procedure for valve-related dysfunction) through discharge or 7 days post-procedure, whichever came first. Clinical follow-up will extend through 5 years.

The primary endpoint was achieved in 9/11 subjects[45]. 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 criteria[44] for device success. The Echocardiography Core Lab concluded that the device failure (mean aortic valve gradient >20 mmHg) resulted from a hyperdynamic state in the subject and noted that the prosthetic valve appeared to be functioning well. Ten (10) of 11 subjects had no in-hospital MACCE; there were no deaths and 1 major stroke. Paravalvular regurgitation at discharge TTE was mild in 2 subjects, trivial in 1 subject, and absent in the other 8 subjects; these outcomes compare favorably with published data[16,24,27,28,46].

To date, data are available through 6 months[47]. There were no additional MACCE events beyond the primary endpoint. While all REPRISE I subjects were NYHA Class II (n=6) or Class III (n=5) at baseline, this distribution was significantly improved at 6 months (6 in Class I, 4 in Class II, 1 in Class III; *P*=0.004). The mean aortic valve gradient was 13.9±3.8 mmHg for the cohort at 6 months, which was below the VARC criterion of 20 mmHg, and there was no moderate or severe paravalvular aortic regurgitation. The results of the REPRISE I feasibility study support the acute safety and performance of the Lotus Valve System.

4.2. *Justification for the Study Design*

As noted above, the Lotus Valve System potentially provides a number of performance and safety features beyond that of earlier TAVR devices. These include a pre-loaded delivery system, early leaflet function to maintain hemodynamic stability during valve deployment, an enhanced ability to place the valve correctly at the first attempt using the radiopaque marker to aid in valve positioning, 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 the decision is made not to implant, and the aforementioned outer seal designed to minimize paravalvular leakage. The anticipated risks and benefits associated both with the Lotus Valve System and with participation in this clinical investigation are summarized in the Investigator

Brochure and in Section 19 of this document. The conclusion of this risk-benefit analysis demonstrates that the known risks associated with the procedure and the specific use of the Lotus Valve System have been mitigated to acceptable limits and are comparable to that associated with existing transcatheter aortic valves. It was also concluded that the aforementioned design features may improve procedural safety. The available sponsor-provided training program and proctorship for physicians further mitigates the risk. The result is a procedure with residual subject risk comparable to that of currently available transcatheter aortic valves and significant 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

5.1. *Lotus Valve System*

The Lotus Valve System (Figure 5.1-1) has two main parts: a bioprosthetic aortic valve implant and a catheter-based delivery system for introduction and delivery of the valve implant. The device is introduced percutaneously via the femoral artery using conventional catheterization techniques. Femoral access using the surgical cut-down approach can also be performed to gain access into the aortic vessel. More detailed product information is contained in the Investigator Brochure and Instructions for Use (IFU).

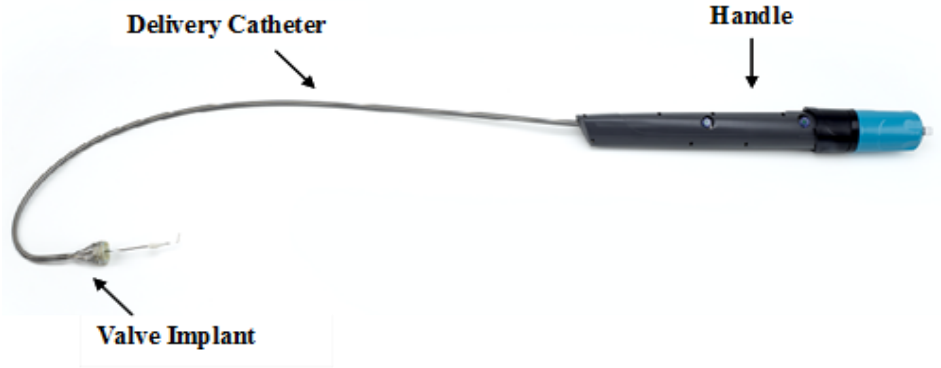


Figure 5.1-1: Lotus™ Valve System

5.1.1. Lotus Valve

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

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

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

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

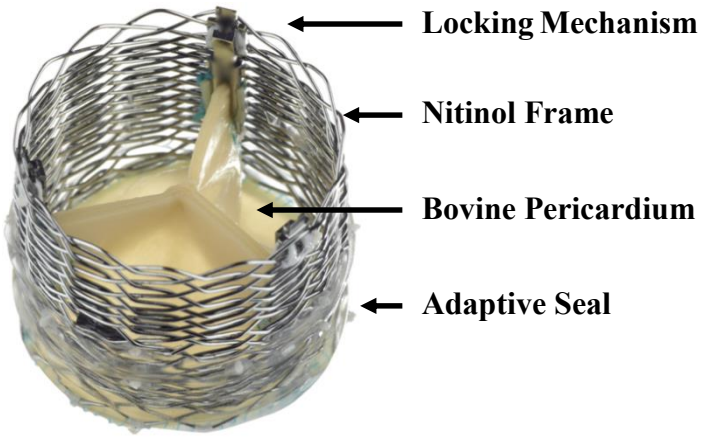


Figure 5.1-2: Lotus Valve Implant

The device is designed so that the radial strength of the frame produces a specified final "as-deployed" diameter (23 mm or 27 mm) when the valve is locked, regardless of the target annulus. The frame height of both valve sizes in the deployed state is approximately 19 mm.

5.1.2. Lotus Delivery System

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

- The catheter is a sheath in which mandrels allowing the shortening, locking, unlocking, and elongation of the valve, as well as its releasing, connect from the handle to the valve.

The catheter has a hydrophilic coating to facilitate the insertion. The tip of the catheter seats on the shoulder of a nosecone to provide a smooth transition.

- The handle is shown in
- Figure 5.1-3.
  - The handle has 3 ports; 2 of the ports are for flushing purposes and one is the Guidewire Port.
  - The Control Knob at the proximal end of the handle is the primary control used to deploy the valve. It operates both the sheathing/unsheathing function as well as the locking/unlocking function.
    - The sheathing/unsheathing capability allows the implant to be pulled into or pushed out of the outer catheter.
    - The locking function shortens the valve implant into the locked configuration; the unlocking function elongates the valve.
  - The Release Collar is used when the operator is ready to release the valve. A sliding door covers the collar to avoid inadvertent premature release.

Figure 5.1-3: Lotus Valve Delivery System – Handle

5.2. *Intended Use*

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

5.3. *Device Labeling*

The study Manual of Operations includes the IFU for the Lotus Valve System. 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
- Part/Reference number
- Lot number (matches the lot number on the handle)
- Valve size
- Expiration (use by) date (labeled as month/year, device not to be used after the last day of the indicated month)
- Temperature storage requirements

The following statement appears on the label.

CAUTION: Exclusively for Clinical Investigations.

Device labeling will be provided in local language(s) as per respective national regulations.

6. Objectives

The objective of the REPRISE II study is to evaluate the safety and performance of the Lotus™ Valve System for transcatheter aortic valve replacement (TAVR) in symptomatic subjects with severe calcific aortic stenosis who are considered high risk for surgical valve replacement.

7. Endpoints

7.1. *Primary Endpoints*

The primary device performance endpoint is the mean aortic valve pressure gradient at 30 days post implant as measured by echocardiography and assessed by an independent core laboratory. The primary analysis population will be the subject population implanted with the

Lotus Valve. Outcomes in this as-treated subject population in the main trial cohort (N=120) will be compared to a performance goal (PG; see Section 12.1.1.1).

The primary safety endpoint is all-cause mortality at 30 days after the implant procedure. The primary safety endpoint will be evaluated on an intention-to-treat (ITT) basis (all subjects enrolled, whether or not a study device is implanted). Outcomes in the combined main and extended trial cohort (N=250) will be compared to a PG (see Section 12.1.1.3).

7.2. *Secondary Endpoints*

Secondary endpoints are listed below and will be evaluated on an ITT basis. Definitions can be found in Table 26.2-1.

- Effective orifice area at 30 days as measured by echocardiography and assessed by an independent core laboratory
- Device performance endpoints peri- and post-procedure:
  - Successful vascular access, delivery and deployment of the Lotus Valve System and successful retrieval of the delivery system
  - Successful repositioning (partial or complete resheathing of the Lotus Valve in the catheter and redeployment in a more accurate position within the aortic valve annulus) of the Lotus Valve System if repositioning is attempted
  - Successful retrieval (complete resheathing of the Lotus Valve in the catheter and removal from the body) of the Lotus Valve System if retrieval is attempted
  - Grade of aortic valve regurgitation: paravalvular, central and combined
- Device Success post implant procedure based on the VARC definitions [44,48]

Note: 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.

7.3. *Additional Measurements*

Additional measurements based on the VARC endpoints and definitions (see references [44,48] and Table 26.2-1 in the Appendix for definitions) will be collected peri- and post-procedure, at discharge or 7 days post-procedure (whichever comes first), 30 days, 3 months, 6 months, and 1, 2, 3, 4, and 5 years post index procedure, unless otherwise specified below. Data will be evaluated on an ITT basis.

- Safety endpoints adjudicated by an independent Clinical Events Committee (CEC):
  - Mortality: all-cause, cardiovascular, and non-cardiovascular
  - Stroke: disabling and non-disabling
  - Composite of all-cause mortality and disabling stroke
  - Myocardial infarction (MI): periprocedural ≤ 72 hours post index procedure) and spontaneous (>72 hours post index procedure)

  - Bleeding: life-threatening (or disabling) and major
  - Acute kidney injury (≤7 days post index procedure): based on AKIN System[49,50] Stage 3 (including renal replacement therapy) or Stage 2
  - Major vascular complication
  - Repeat procedure for valve-related dysfunction (surgical or interventional therapy)
  - Hospitalization for valve-related symptoms or worsening congestive heart failure (NYHA class III or IV)
  - New permanent pacemaker implantation resulting from new or worsened conduction disturbances (including left bundle branch block [LBBB] and third degree atrioventricular block)
  - New onset of atrial fibrillation and atrial flutter
  - Coronary obstruction (periprocedural)
  - Ventricular septal perforation (periprocedural)
  - Mitral apparatus damage (periprocedural)
  - Cardiac tamponade (periprocedural)
  - Prosthetic aortic valve malapposition, including valve migration, valve embolization, ectopic valve deployment, or transcatheter aortic valve (TAV)-in-TAV deployment
  - Prosthetic aortic valve thrombosis
  - Prosthetic aortic valve endocarditis
- Prosthetic aortic valve performance as measured by transthoracic echocardiography (TTE) and assessed by an independent core laboratory, including effective orifice area, mean and peak aortic gradients, peak aortic velocity, and grade of aortic regurgitation
- Functional status as evaluated by the following:
  - 5-m gait speed test[51] (at 1 year compared to baseline)
  - New York Heart Association (NYHA) classification
- Neurological status as determined by the following:
  - National Institutes of Health Stroke Scale (NIHSS) at discharge and 1 year
  - Modified Rankin Scale (mRS)
- Health status as evaluated by SF-12 and EQ-5D Quality of Life (QOL) questionnaires[52,53] at baseline; 1 and 6 months; and 1, 3, and 5 years

Note 1: The VARC safety composite at 30 days will be reported. This includes all-cause mortality, all stroke, life-threatening bleeding, acute kidney injury Stage 2 or 3, coronary artery obstruction requiring intervention, major vascular complication, and repeat procedure for valve-related dysfunction.

Note 2: The VARC efficacy composite at 1 year will be reported. This includes all-cause mortality (after 30 days), all stroke, requiring hospitalization for valve-related symptoms or worsening congestive heart failure (NYHA class III or IV), and prosthetic heart valve

dysfunction (mean aortic valve gradient ≥20 mm Hg, effective orifice area ≤0.9-1.1 cm^2 and/or Doppler velocity index [DVI] <0.35, AND/OR moderate or severe prosthetic valve aortic regurgitation [per VARC definition]) .

Note 3: Time-related valve safety composite will be reported. This includes structural valve deterioration (valve-related dysfunction requiring repeat procedure [TAVR or SAVR]), prosthetic valve endocarditis, prosthetic valve thrombosis, thromboembolic events (e.g., stroke), and VARC bleeding (unless clearly unrelated to valve therapy based on investigator assessment).

Note 4: In the main trial cohort (N=120), for subjects diagnosed with a neurological event (e.g., stroke, transient ischemic attack), a neurological physical exam, NIHSS assessment, and mRS must be performed after the event; mRS must also be administered at 90 days post-neurological event (see Table 11.1-1). Among the 130 subjects subsequently enrolled (extended trial cohort), for subjects diagnosed with a neurological event, NIHSS assessment and mRS must be performed after the event; mRS must also be administered at 90 days post-neurological event; the neurological physical exam is not required (see Table 11.1-2).

Note 5: The VARC clinical efficacy composite includes the need for hospitalization associated with valve-related symptoms or worsening congestive heart failure (CHF) as a basis for calculation of a "days alive outside the hospital" endpoint. This includes 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.

8. Design

8.1. *Scale and Duration*

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

All subjects implanted will be followed at baseline, peri- and post-procedure, at discharge or 7 days post-procedure (whichever comes first), 30 days, 3 months, 6 months, and then annually for up to 5 years post-procedure. Subjects who do not have the Lotus Valve implanted will be assessed through 30 days post procedure for safety/adverse events.

The REPRISE II study will be conducted in accordance with the International Standard ISO 14155: 2011; ethical principles that have their origins in the Declaration of Helsinki; the relevant parts of the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practices (GCP); and pertinent individual country/state/local laws and regulations. See Section 11 below for additional information on study design and data collection.

8.2. *Treatment Assignment*

Screening materials from eligible subjects who are identified by the investigators as having met the inclusion and exclusion criteria (see below Table 9.2-1 and Table 9.3-1, respectively) and who provide written informed consent, will be reviewed by a Case Review Committee (CRC, see Section 22.2) to assess and confirm suitability of subjects for enrollment. ***In all enrolled subjects an attempt will be made to implant a single Lotus Valve.***

8.2.1. Treatment

The test device is the Lotus Valve System, which consists of a bioprosthetic bovine pericardial aortic valve and a delivery system. The commercially available Lotus Introducer Set is used as an accessory in the procedure. See Section 5 for a detailed description and information on device sizes.

8.3. *Study Design Justification*

In order to support the stated objectives of this study (see Section 6) while also limiting the potential exposure of study subjects to risk, a total of 120 subjects will be enrolled in the main trial cohort at up to 15 centers in these possible countries: Australia, France, Germany and United Kingdom. Planned interim analyses based on the primary endpoint at 30 days post-implant procedure will be performed on the first 40 and 60 enrolled subjects and a final analysis will be conducted on the main trial cohort (N=120). Subsequently, up to 130 additional subjects will be enrolled at up to 21 centers in Australia and European countries and a statistically powered analysis based on the primary safety endpoint will be performed on the combined main and extended trial cohort (250 subjects). In addition to the risk-benefit analysis noted in Section 4.2 (see also Section 19), ongoing dynamic data safety monitoring will be performed throughout the trial to minimize risk to subjects. All implanted subjects will be followed for 5 years post index procedure.

9. Subject Selection

9.1. *Study Population and Eligibility*

The study will include subjects presenting with symptomatic, calcific aortic valve stenosis who are considered at high risk for surgical valve replacement. Prior to being eligible for the REPRISE II study, a subject must meet all of the inclusion criteria (Section 9.2) and none of

the exclusion criteria (Section 9.3). All subjects will then be reviewed by the CRC to confirm eligibility and suitability for enrollment in the study.

9.2. *Inclusion Criteria*

Subjects who meet all of the following criteria (see Table 9.2-1) may be given consideration for inclusion in this clinical investigation, provided no exclusion criterion (see Section 9.3) is met.

Table 9.2-1: Inclusion Criteria

Inclusion Criteria	IC1.	Subject is ≥70 years of age
	IC2.	Subject has documented calcific native aortic valve stenosis with an initial aortic valve area (AVA) of <1.0 cm^2 (or AVA index of <0.6 cm^2/m^2) and either a mean pressure gradient >40 mm Hg or a jet velocity >4 m/s, as measured by echocardiography.
	IC3.	Subject has a documented aortic annulus size between ≥20 and ≤27 mm based on pre-procedure diagnostic imaging
	IC4.	Subject has symptomatic aortic valve stenosis with NYHA Functional Class ≥ II.
	IC5.	Subject is considered high risk for surgical valve replacement based on at least one of the following: – STS score ≥8%, and/or – Agreement by the heart team (which must include an in-person evaluation by an experienced cardiac surgeon) that subject is at high operative risk of serious morbidity or mortality with surgical valve replacement.
	IC6.	Heart team (which must include an experienced cardiac surgeon) assessment that the subject is likely to benefit from valve replacement
	IC7.	Subject (or legal representative) understands 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.

Abbreviations: AVA=aortic valve area; NYHA=New York Heart Association; STS= Society of Thoracic Surgeons

9.3. *Exclusion Criteria*

Subjects who meet any one of the following criteria (Table 9.3-1) will be excluded from this clinical study.

Table 9.3-1: Exclusion Criteria

Exclusion Criteria	EC1.	Subject has a congenital unicuspid or bicuspid aortic valve.
	EC2.	Subject with an acute myocardial infarction within 30 days of the index procedure (defined as Q-wave MI or non–Q-wave MI with total CK elevation ≥ twice normal

Table 9.3-1: Exclusion Criteria

	in the presence of CK-MB elevation and/or troponin level elevation). EC3. Subject has had a cerebrovascular accident or transient ischemic attack within the past 6 months, or has any permanent neurologic defect prior to study enrollment. EC4. Subject is on dialysis or has serum creatinine level >3.0 mg/dL or 265 µml/L. EC5. Subject has a pre-existing prosthetic heart valve (aortic or mitral) or a prosthetic ring in any position. EC6. Subject has ≥3+ mitral regurgitation, ≥3+ aortic regurgitation or ≥3+ tricuspid regurgitation (i.e., subject cannot have more than moderate mitral, aortic or tricuspid regurgitation). EC7. Subject has a need for emergency surgery for any reason. EC8. Subject has a history of endocarditis within 12 months of index procedure or evidence of an active systemic infection or sepsis. EC9. Subject has echocardiographic evidence of intra-cardiac mass, thrombus or vegetation. EC10. Subject has Hgb <9 g/dL, platelet count <50,000 cells/mm^3 or >700,000 cells/mm^3, or white blood cell count <1,000 cells/mm^3. EC11. Subject is receiving chronic (≥72 hours) anticoagulation therapy (e.g., warfarin, dabigatran, etc.), and cannot tolerate concomitant therapy with aspirin or clopidogrel (subjects who require chronic anticoagulation must additionally be able to be treated with either aspirin or clopidogrel).* EC12. Subject has active peptic ulcer disease or gastrointestinal bleed within the past 3 months, other bleeding diathesis or coagulopathy or will refuse transfusions. EC13. Subject has known hypersensitivity to contrast agents that cannot be adequately pre-medicated, or has known hypersensitivity to aspirin, all thienopyridines, heparin, nickel, titanium, or polyurethanes. EC14. Subject has a life expectancy of less than 12 months due to non-cardiac, co-morbid 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 procedure (including balloon aortic valvuloplasty) within 30 days prior to the index procedure (except for pacemaker implantation which is allowed). EC17. Subject has untreated coronary artery disease, which in the opinion of the treating physician, is clinically significant and requires revascularization. EC18. Subject has documented left ventricular ejection fraction <30%. EC19. Subject is in cardiogenic shock or has hemodynamic instability requiring inotropic support or mechanical support devices. EC20. Subject has severe peripheral vascular disease (including aneurysm defined as maximal luminal diameter >5 cm or with documented presence of thrombus, marked tortuosity, narrowing of the abdominal aorta, severe unfolding of the thoracic aorta or thick [>5 mm] protruding or ulcerated atheroma in the aortic arch) or symptomatic carotid or vertebral disease. EC21. Femoral artery lumen of <6.0 mm for subjects requiring 23 mm valve size or <6.5 mm for subjects requiring 27 mm valve size, or severe iliofemoral tortuosity or calcification that would prevent safe placement of the introducer sheath. EC22. Current problems with substance abuse (e.g., alcohol, etc.).

Table 9.3-1: Exclusion Criteria

	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.

* An alternative P2Y12 inhibitor (e.g., ticlopidine) may be prescribed if subject is allergic to or intolerant of clopidogrel.

Abbreviation: AV= atrioventricular; CK=creatine kinase; MI=myocardial infarction

10. Subject Accountability

10.1. *Point of Enrollment*

Subjects 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 Valve System into the subject's femoral artery.

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. 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.

11. Study Methods

11.1. *Data Collection*

The study event schedules are shown diagrammatically and discussed in Figure 11.1-1 and Table 11.1-1 for the main trial cohort (N=120) and in Figure 11.1-2 and Table 11.1-2 for the subsequently enrolled 130 additional subjects (extended trial cohort).

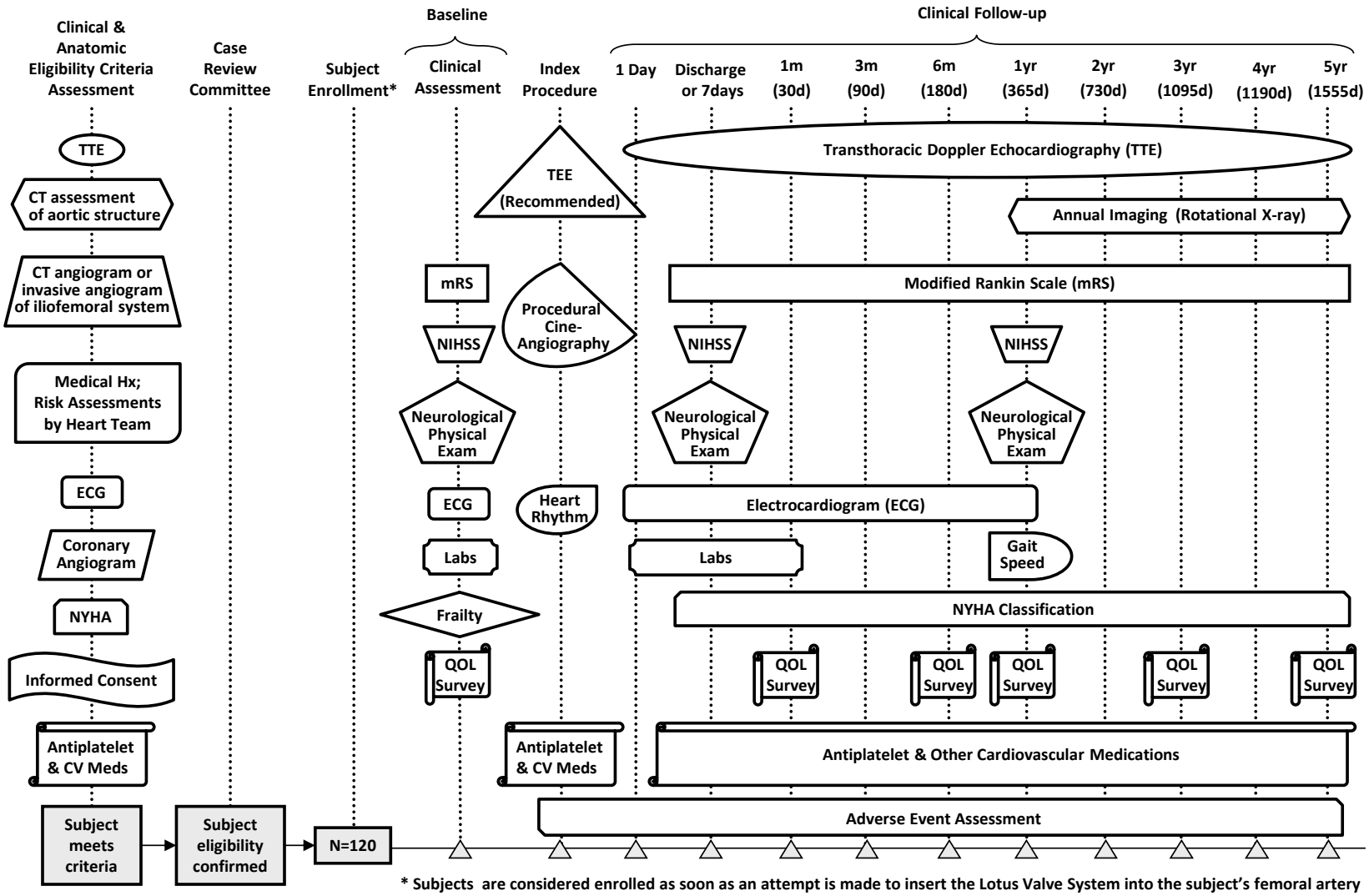


Figure 11.1-1: REPRISE II Study Design – Main Trial Cohort

Table 11.1-1: Study Event Schedule – Main Trial Cohort

Assessment	Screening[a]	Baseline[b]	Procedure	Within 1 Day Post-procedure	Prior to Discharge or 7 Days Post-Procedure	30 Days[c] (±7 Days) Office Visit	3 Months[c] (±14 Days) Office Visit	6 Months[c] (±30 Days) Office Visit	12 Months[c] (±45 Days) Office Visit	24–60 Months[c] [Annual] (±45 Days) Office Visit
Signed Informed Consent Form[d]	X									
Demographics and medical history, including cardiac, neurological, renal (e.g., creatinine) and peripheral disease	X									
NYHA Classification	X				X	X	X	X	X	X
Neurological physical exam[e]		X			X				X	
NIHSS[e]		X			X				X	
Modified Rankin Scale[e]		X			X	X	X	X	X	X
12-lead ECG[f]	X	X	X[f]	X	X	X	X	X	X	
Laboratory tests[g]		X		X		X				
Risk assessments[h]	X									
Frailty, disability and comorbidity[i]		X							X	
Antiplatelet and other cardiovascular medications	X		X		X	X	X	X	X	X
TTE[j]	X				X	X	X	X	X	X
TEE[k]			X							
Coronary angiogram[l]	X									
CT angiogram of aortic structure[m]	X									

Table 11.1-1: Study Event Schedule – Main Trial Cohort

Assessment	Screening[a]	Baseline[b]	Procedure	Within 1 Day Post-procedure	Prior to Discharge or 7 Days Post-Procedure	30 Days[c] (±7 Days) Office Visit	3 Months[c] (±14 Days) Office Visit	6 Months[c] (±30 Days) Office Visit	12 Months[c] (±45 Days) Office Visit	24–60 Months[c] [Annual] (±45 Days) Office Visit
CT angiogram or invasive angiogram of iliofemoral system[n]	X									
Annual imaging (rotational X-ray)[o]									X	X
QOL surveys[p]		X				X		X	X	X[q]
Procedural cine-angiography (including post-deployment aortogram)[r]			X							
AE and ADE assessments[s]			X	X	X	X	X	X	X	
Device deficiencies, SAE, SADE, USADE, and CEC event assessment[t]			X	X	X	X	X	X	X	X

a: It is recommended that screening occur no later than 10 days prior to the index procedure (unless otherwise specified); results from these assessments should be submitted to the CRC at least 10 days prior to the planned procedure to allow for adequate scheduling of subject review at a CRC meeting.

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

c: All follow-up dates will be calculated from the date of the index procedure. Visits must be an office/clinical visit, but may be done in-hospital should the subject be admitted at the time. Subjects who are enrolled but do not receive a Lotus Valve will be followed for 30 days to assess for safety but do not need to have protocol required TTE, ECG, or laboratory tests or complete quality of life questionnaires.

d: 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.

e: Neurological physical examination must be performed by a neurologist or neurology fellow. NIHSS and mRS must be performed by certified personnel (external certification for NIHSS; internal or external certification for mRS). The assessors should be independent (not involved with the care of study subjects). For subjects diagnosed with a neurological event (e.g., stroke, transient ischemic attack), a neurological physical exam, mRS, and NIHSS must be performed after the event; mRS must also be administered at 90 days post-neurological event.

f: All baseline and post-procedure 12-lead ECGs must be performed according to the ECG Core Laboratory guidelines (see study Manual of Operations). Heart rhythm

Table 11.1-1: Study Event Schedule – Main Trial Cohort

Assessment	Screening[a]	Baseline[b]	Procedure	Within 1 Day Post-procedure	Prior to Discharge or 7 Days Post-Procedure	30 Days[c] (±7 Days) Office Visit	3 Months[c] (±14 Days) Office Visit	6 Months[c] (±30 Days) Office Visit	12 Months[c] (±45 Days) Office Visit	24–60 Months[c] [Annual] (±45 Days) Office Visit

strip must be obtained between balloon aortic valvuloplasty and before Lotus Valve insertion.

g: Laboratory tests at baseline include CBC, platelet count, LDH, haptoglobin, 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. At 30 days, laboratory tests include LDH and haptoglobin.

h: Consists of STS score (2.73), euroSCORE 2011, and heart team assessment including an in-person evaluation by a cardiac surgeon.

i: Frailty, disability and comorbidity risk assessments must also be captured at baseline: nutritional assessment (albumin, body mass index), cognitive function (Mini-Cognitive Assessment for Dementia), strength and balance (use of wheelchair, gait speed to walk 5 meters, number of falls in the past 6 months, maximal grip strength), activities of daily living (Katz Index), and comorbidity (Charlson Index); at 1 year, gait speed to walk 5 meters must be assessed again.

j: Transthoracic echocardiogram (TTE) is required, including assessment of effective orifice area, peak systolic and mean aortic valve gradient pressure, aortic regurgitation assessment, and LVEF. Screening TTE must be performed within 60 days prior to 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. All TTEs must be performed according to the Echocardiography Core Laboratory procedure guidelines (see study Manual of Operations).

k: TEE is recommended but not required during the implant procedure.

l: A coronary angiogram must be performed within 365 days prior to the index procedure. If there is concern regarding the current extent of coronary artery disease or aortic stenosis, the Case Review Committee may recommend a repeat study closer to the time of enrollment.

m: Computed tomography (CT) angiogram of the entire aortic structure, including the aortic root (from superior to the aortic arch to inferior to the cardiac apex) and from descending to abdominal aorta, must be performed within 180 days prior to the index procedure (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 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 meeting where results will be reviewed to confirm subject's eligibility.

n: Either a CT angiogram or invasive angiogram of iliofemoral system must be performed within 180 days prior to the index procedure (and should be performed within 90 days if possible) for complete visualization of the iliac and femoral arteries to assess for dimensions, tortuosity and calcification. CT angiogram of the iliofemoral system should be performed per the procedure guidelines (see study Manual of Operations) and sent to the CT Core Laboratory with the screening CT angiogram of the aortic structure.

o: Annual imaging using rotational x-ray angiography to assess for structural valve frame integrity must be performed. Please refer to the Imaging Core Laboratory procedure guidelines (see study Manual of Operations). Results must be forwarded to the CT/X-Ray Core Laboratory for analysis. If additional imaging is performed (e.g., cardiac CT or MRI scan), data may be provided for analysis.

p: Includes the SF-12 and EQ-5D QOL questionnaires. Baseline QOLs should be performed within 30 days prior to the index procedure.

Table 11.1-1: Study Event Schedule – Main Trial Cohort

Assessment	Screening[a]	Baseline[b]	Procedure	Within 1 Day Post-procedure	Prior to Discharge or 7 Days Post-Procedure	30 Days[c] (±7 Days) Office Visit	3 Months[c] (±14 Days) Office Visit	6 Months[c] (±30 Days) Office Visit	12 Months[c] (±45 Days) Office Visit	24–60 Months[c] [Annual] (±45 Days) Office Visit

q: QOL survey at 36 and 60 months.

r: Procedural cine-angiogram including the final post-deployment aortogram of the ascending aorta should be sent to the CT/X-Ray Core Laboratory for analysis.

s: 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 30-day follow-up.

t: Device deficiencies (for the Lotus Valve System), SAEs, SADEs, USADEs, and CEC events will be monitored and reported to Boston Scientific for all enrolled subjects from the time of enrollment through termination of the study. For subjects who do not receive the study device, the mentioned events will be monitored through 30 days post-index procedure. Please refer to Section 7.3 for a list of CEC events and Table 26.2-1 for definitions of these events, which specify data required for CEC adjudication.

Abbreviations: AE=adverse event; ADE=adverse device effect; AKI=acute kidney injury; CBC=complete blood count; CEC=Clinical Events Committee; CK-MB=creatine kinase-myoglobin band; CRC=Case Review Committee; CT=computed tomography; ECG=electrocardiogram; 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; USADE=unanticipated serious adverse device effect

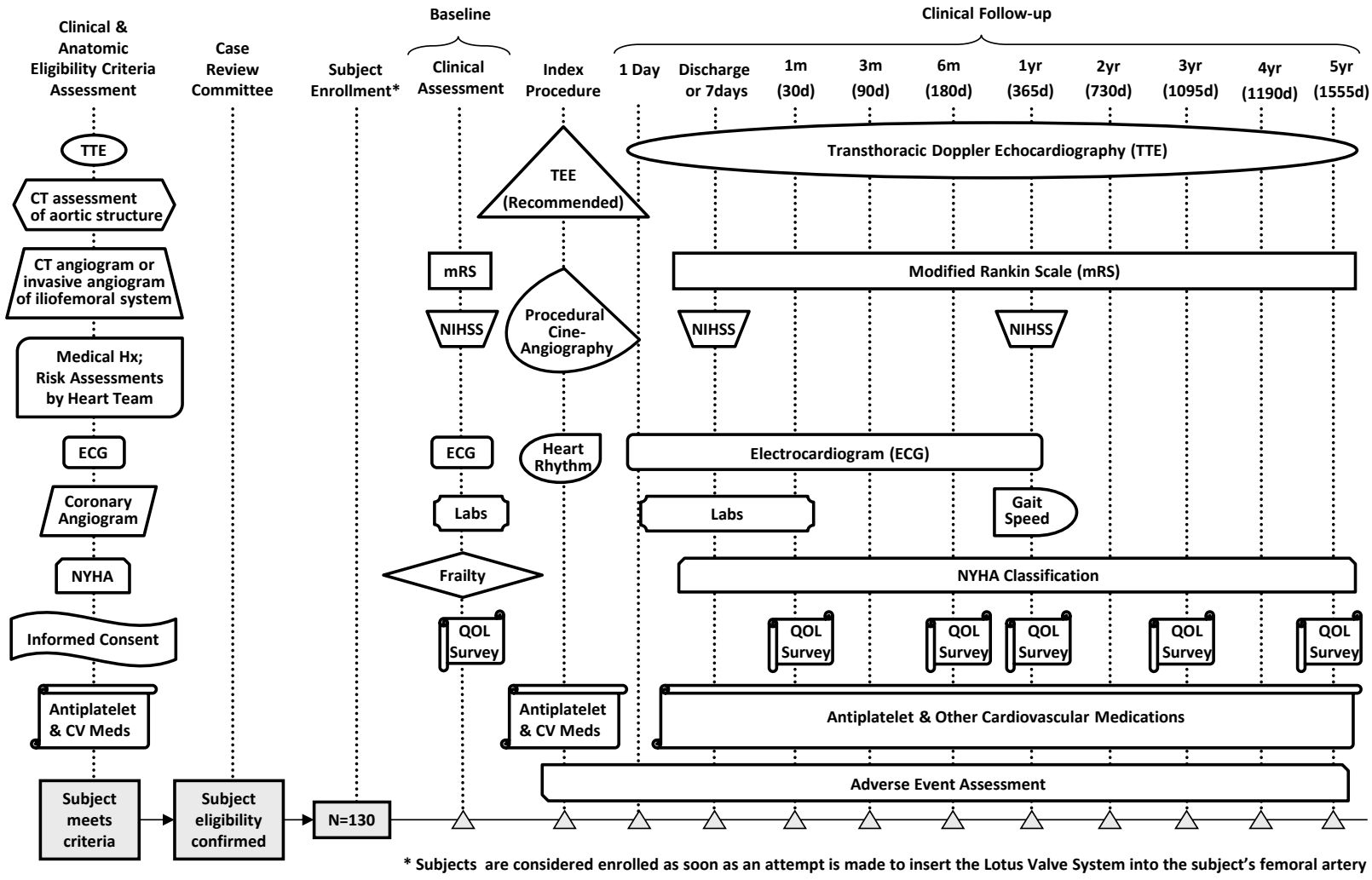


Figure 11.1-2: REPRISE II Study Design – Extended Trial Cohort

Table 11.1-2: Study Event Schedule – Extended Trial Cohort

Assessment	Screening[a]	Baseline[b]	Procedure	Within 1 Day Post-procedure	Prior to Discharge or 7 Days Post-Procedure	30 Days[c] (±7 Days) Office Visit	3 Months[c] (±14 Days) Office Visit	6 Months[c] (±30 Days) Office Visit	12 Months[c] (±45 Days) Office Visit	24–60 Months[c] [Annual] (±45 Days) Office Visit
Signed Informed Consent Form[d]	X									
Demographics and medical history, including cardiac, neurological, renal (e.g., creatinine) and peripheral disease	X									
NYHA Classification	X				X	X	X	X	X	X
NIHSS[e]		X			X				X	
Modified Rankin Scale[e]		X			X	X	X	X	X	X
12-lead ECG[f]	X		X[f]	X	X	X	X	X	X	
Laboratory tests[g]		X		X		X				
Risk assessments[h]	X									
Frailty, disability and comorbidity[i]	X								X	
Antiplatelet and other cardiovascular medications	X		X		X	X	X	X	X	X
TTE[j]	X				X	X	X	X	X	X
TEE[k]			X							
Coronary angiogram[l]	X									
CT angiogram of aortic structure[m]	X									
CT angiogram or invasive angiogram of iliofemoral system[n]	X									
QOL surveys[o]		X				X		X	X	X[p]

Table 11.1-2: Study Event Schedule – Extended Trial Cohort

Assessment	Screening[a]	Baseline[b]	Procedure	Within 1 Day Post-procedure	Prior to Discharge or 7 Days Post-Procedure	30 Days[c] (±7 Days) Office Visit	3 Months[c] (±14 Days) Office Visit	6 Months[c] (±30 Days) Office Visit	12 Months[c] (±45 Days) Office Visit	24–60 Months[c] [Annual] (±45 Days) Office Visit
Procedural cine-angiography (including post-deployment aortogram and rotational angiogram)[q]			X							
AE and ADE assessments[r]			X	X	X	X	X	X	X	
Device deficiencies, SAE, SADE, USADE, and CEC event assessment[s]			X	X	X	X	X	X	X	X

a: It is recommended that screening occur no later than 10 days prior to the index procedure (unless otherwise specified); results from these assessments should be submitted to the CRC at least 10 days prior to the planned procedure to allow for adequate scheduling of subject review at a CRC meeting.

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

c: All follow-up dates will be calculated from the date of the index procedure. Visits must be an office/clinical visit, but may be done in-hospital should the subject be admitted at the time. Subjects who are enrolled but do not receive a Lotus Valve will be followed for 30 days to assess for safety but do not need to have protocol required TTE, ECG, or laboratory tests or complete quality of life questionnaires.

d: 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.

e: NIHSS and mRS must be performed by certified personnel (external certification for NIHSS; internal or external certification for mRS). The assessors should be independent (not involved with the care of study subjects). For subjects diagnosed with a neurological event (e.g., stroke, transient ischemic attack), mRS, and NIHSS must be performed after the event; mRS must also be administered at 90 days post-neurological event.

f: All pre-(screening or baseline) and post-procedure 12-lead ECGs must be performed according to the ECG Core Laboratory guidelines (see study Manual of Operations). Heart rhythm strip must be obtained between balloon aortic valvuloplasty and before Lotus Valve insertion.

g: Laboratory tests at baseline include CBC, platelet count, LDH, haptoglobin, 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. At 30 days, laboratory tests include LDH and haptoglobin.

h: Consists of STS score 2.73, euroSCORE 2011, and heart team assessment including an in-person evaluation by a cardiac surgeon.

i: Frailty, disability and comorbidity risk assessments must also be captured prior to the implant procedure: nutritional assessment (albumin, body mass index), cognitive

Table 11.1-2: Study Event Schedule – Extended Trial Cohort

Assessment	Screening[a]	Baseline[b]	Procedure	Within 1 Day Post-procedure	Prior to Discharge or 7 Days Post-Procedure	30 Days[c] (±7 Days) Office Visit	3 Months[c] (±14 Days) Office Visit	6 Months[c] (±30 Days) Office Visit	12 Months[c] (±45 Days) Office Visit	24–60 Months[c] [Annual] (±45 Days) Office Visit

function (Mini-Cognitive Assessment for Dementia), strength and balance (use of wheelchair, gait speed to walk 5 meters, number of falls in the past 6 months, maximal grip strength), activities of daily living (Katz Index), and comorbidity (Charlson Index); at 1 year, gait speed to walk 5 meters must be assessed again.

j: Transthoracic echocardiogram (TTE) is required, including assessment of effective orifice area, peak systolic and mean aortic valve gradient pressure, aortic regurgitation assessment, and LVEF. Screening TTE must be performed within 60 days prior to 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. All TTEs must be performed according to the Echocardiography Core Laboratory procedure guidelines (see study Manual of Operations).

k: TEE is recommended but not required during the implant procedure.

l: A coronary angiogram must be performed within 365 days prior to the index procedure. 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.

m: CT angiogram of the entire aortic structure, including the aortic root (from superior to the aortic arch to inferior to the cardiac apex) and from descending to abdominal aorta, must be performed within 180 days prior to the index procedure (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 meet the CT 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 meeting where results will be reviewed to confirm subject's eligibility.

n: Either a CT angiogram or invasive angiogram of iliofemoral system must be performed within 180 days prior to the index procedure (and should be performed within 90 days if possible) for complete visualization of the iliac and femoral arteries to assess for dimensions, tortuosity and calcification. CT angiogram of the iliofemoral system should be performed per the procedure guidelines (see study Manual of Operations) and sent to the CT Core Laboratory with the screening CT angiogram of the aortic structure.

o: Includes the SF-12 and EQ-5D QOL questionnaires. Baseline QOLs should be performed within 30 days prior to the index procedure.

p: QOL survey at 36 and 60 months.

q: Procedural cine-angiogram including the final post-deployment aortogram of the ascending aorta (including recommended rotational angiogram of the valve frame) should be sent to the CT/X-Ray Angio 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 30-day follow-up.

s: Device deficiencies (for the Lotus Valve System), SAEs, SADEs, USADEs, and CEC events will be monitored and reported to Boston Scientific for all enrolled subjects from the time of enrollment through termination of the study. For subjects who do not receive the study device, the mentioned events will be monitored through 30 days post-index procedure. Please refer to Section 7.3 for a list of CEC events and Table 26.2-1 for definitions of these events, which specify data required for CEC adjudication.

Abbreviations: AE=adverse event; ADE=adverse device effect; AKI=acute kidney injury; CBC=complete blood count; CEC=Clinical Events Committee;

Table 11.1-2: Study Event Schedule – Extended Trial Cohort

Assessment	Screening[a]	Baseline[b]	Procedure	Within 1 Day Post-procedure	Prior to Discharge or 7 Days Post-Procedure	30 Days[c] (±7 Days) Office Visit	3 Months[c] (±14 Days) Office Visit	6 Months[c] (±30 Days) Office Visit	12 Months[c] (±45 Days) Office Visit	24–60 Months[c] [Annual] (±45 Days) Office Visit

CK-MB=creatine kinase-myoglobin band; CRC=Case Review Committee; CT=computed tomography; ECG=electrocardiogram; LDH=lactate dehydrogenase; LV=left ventricle; 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; USADE=unanticipated serious adverse device effect

11.2. *Study Candidate Screening*

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

Clinical assessment and evaluation as well as all collected tests and images (e.g., echocardiography, computerized tomography [CT], angiography) performed in preparation for TAVR will be reviewed by the CRC (see Section 8.2 and Section 22.2). The CRC will be comprised of the Study Principal Investigator (PI) and other investigators experienced with TAVR along with the Sponsor to review and confirm subject eligibility for enrollment.

11.3. *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 Informed Consent form (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 Institutional Review Board (IRB)/Independent Ethics Committee (IEC) 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 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.

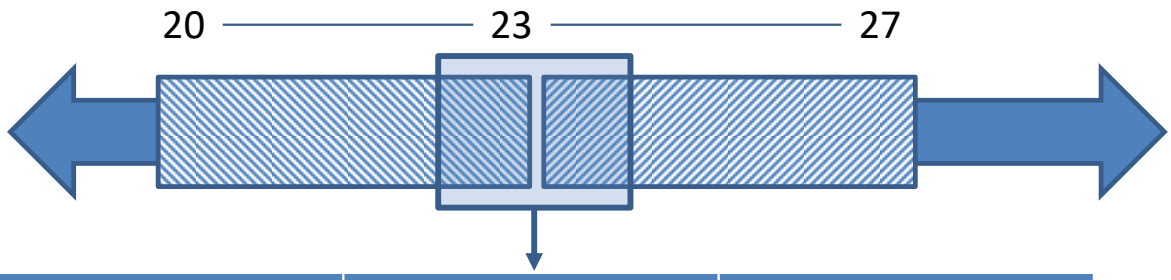
11.4. *Screening Assessments*

The following screening tests and procedures must be performed and submitted to the Case Review Committee for evaluation to confirm a subject's eligibility into the study. These assessments should be completed no later than 10 days prior to the planned procedure, unless otherwise specified below. The results from these assessments should be submitted to the CRC at least 10 days prior to the planned procedure to allow for adequate scheduling of subject review at a CRC meeting. It is planned that the CRC meeting will take place at least weekly to ensure timely review and confirmation of subject eligibility. This will accommodate a second review before the planned procedure should this be needed.

Sites will be trained on the screening process as detailed in the REPRISE II Training Plan (see Section 17.4.1). Specific data points will be collected in the REPRISE II 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
  - Risk assessments: STS Score (2.73), euroSCORE 2011, heart team assessment including an in-person evaluation by a cardiac surgeon, and any frailty assessments
  - Current antiplatelet and other cardiovascular medications
  - 12-lead electrocardiogram (ECG)
- Imaging assessments
  - Within 60 days prior to the procedure, TTE (2-D, M-Mode, and color) must be carried out. The evaluation should include assessment of effective orifice area, peak systolic and mean aortic valve gradient pressure, aortic regurgitation assessment, mitral regurgitation, LVEF, left ventricular end-diastolic and end-systolic diameter, tricuspid regurgitation (TR) jet velocity, and left atrial (LA) volume. Other echocardiographic measurements include, but are not limited to, aortic valve diameter, left ventricular outflow tract, diameter, Sinus of Valsalva diameter, annulus to ventricular apex length, mitral hinge point to apex length. TTEs must be performed according to the Echocardiography Core Laboratory procedure guidelines (see study Manual of Operations). All TTEs for enrolled subjects must be sent to the Echocardiography Core Laboratory for independent analyses.
  - A coronary angiogram must be performed within 365 days prior to the index procedure. If there is concern regarding the current extent of coronary artery disease or aortic stenosis, the Case Review Committee 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 entire aortic structure, including the aortic root (from superior to the aortic arch to inferior to the cardiac apex) and from the descending to the abdominal aorta, must be performed 180 days prior to the index procedure 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 forwarded in advance to the Core Laboratory for detailed measurements and independent analyses, which will be reviewed by the CRC to confirm subject's eligibility.
- Either a CT or invasive angiogram of the iliofemoral system must be performed within 180 days prior to the index procedure (and should be performed within 90 days if possible) 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 sent to the CT Core Laboratory with the screening CT angiogram of the aortic structure for independent measurements and review by the CRC to confirm subject's eligibility.
- Figure 11.4-1 shows a list of assessment considerations dependent upon a subject's anatomy in order to determine which Lotus Valve size should be implanted for those subjects who might be a candidate for either valve size.



Small	Assessment Consideration	Large
<6.5mm	Femoral Size	≥6.5 mm
Smaller	Subject Size (ht/wt/BMI)	Larger
Very Heavy	Calcification	Moderate
Smaller	Sinus Dimension	Larger
Smaller	Left Ventricular Outflow Tract	Larger
Borderline	Coronary Height	Adequate
Lesser	Eccentricity	Greater

Figure 11.4-1: Assessment Considerations for Lotus Valve Size Selection

11.5. *Baseline Assessments*

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

- Confirmation of eligibility criteria
- Neurological physical examination required in the main trial cohort, which must be performed by a neurologist or neurology fellow (see Table 11.1-1); assessors should be independent (not involved with the care of study subjects). A neurological physical examination is not required in the extended trial cohort (see Table 11.1-2).

- NIH Stroke Scale (NIHSS), which must be performed by certified personnel (external certification); assessors should be independent (not involved with the care of study subjects)
- Modified Rankin Scale score, which must be performed by certified personnel (external or internal certification); assessors should be independent (not involved with the care of study subjects).
- Laboratory tests
  - Complete blood count (CBC) with platelets
  - LDH
  - Haptoglobin
  - Serum creatinine
  - Cardiac enzymes (CK is required, CKMB or troponin if CK is elevated)
- The following frailty, disability, and comorbidity assessments at screening and/or baseline will be collected prospectively in the REPRISE II study.
  - Nutritional assessment
    - Albumin
    - Body Mass Index from the physical exam
  - Cognitive function: Mini-Cognitive Assessment for Dementia[54,55] where a subject is instructed to listen carefully to and recall three unrelated words (1 point for each recalled word) and to draw a clock with hands specific to a time given (2 points for a normal clock and no points for an abnormal clock).
  - Strength and balance
    - Use of wheelchair
    - Gait speed as measured by a stopwatch for a subject to walk 5 meters (3 measures averaged)[56-58]
    - Number of falls in the past 6 months
    - Maximal grip strength (kg) in the dominant hand (3 measures averaged), using a Jamar hand-held dynamometer[59]
  - Activities of daily living: Katz Index[55,60] 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.
  - Comorbidity: Charlson Index contains 19 categories of comorbidity and assigns a weighted value to each subject's comorbidity based on the risk of 1-year mortality[55,61].
- 12-lead electrocardiogram (ECG) at screening and/or baseline must be performed according to the ECG Core Laboratory guidelines (see study Manual of Operations) and forwarded to Core Laboratory for analysis.
- Quality Of Life (QOL) Surveys: SF-12 and EQ-5D QOL Questionnaires[52,53] must be administered to the subject within 30 days prior to the procedure.

11.6. *Preprocedure Medications*

- Antiplatelet Therapy:

  Subjects must be treated with aspirin and a thienopyridine prior to implantation of the Lotus Valve.

  Aspirin

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

  Clopidogrel

  A loading dose of clopidogrel (recommended dose of ≥300 mg) is required for subjects who have not been taking clopidogrel for ≥72 hours at the time of the index procedure. The loading dose must be administered prior to the implant procedure or immediately after.

  Note 1*:* An alternative P2Y12 inhibitor (e.g., ticlopidine) may be prescribed as an alternative if subject is allergic to or intolerant of clopidogrel.

  Note 2: If the study-specific dosages and durations for antiplatelet medications conflict with country-specific labeling for the medications, the country-specific labeling should take precedence.

  Note 3: If a subject requires chronic anticoagulation (e.g., warfarin, dabigatran, etc.), either clopidogrel or aspirin is required prior to implant procedure (but both aspirin and clopidogrel are not required).

- 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 the local practice. The choice of antibiotic drug is left to the investigator's discretion.

11.7. *Index Procedure*

11.7.1. Percutaneous Procedure for Delivering the Lotus Device

The preparation of the subject for the percutaneous procedure will be performed following standard techniques. The Lotus Introducer is then prepared and introduced into the subject's femoral artery, as described in the Lotus Introducer IFU.

11.7.2. Valvuloplasty

A balloon valvuloplasty on the native valve following standard techniques must be performed with an adequately sized valvuloplasty balloon (avoid oversizing). In the event of

a significant waist and the subject is hemodynamically stable, balloon valvuloplasty should be repeated as needed to achieve a resulting aortic annulus in which a valvuloplasty balloon can be fully inflated with no significant waist. If a significant waist remains after repeated valvuloplasty, it is strongly recommended that appropriate valve size be reconsidered or, if annulus size is within the lower measurement of the annulus size, that the Lotus Valve not be implanted. The subject should be treated according to the Investigator's discretion and standard of care. If the subject is not implanted with the Lotus Valve, then the subject will be followed for 30 days post-procedure.

Careful attention should be paid to the position of the guidewire throughout the procedure. Prior to introduction of the Lotus Valve System, the subject's hemodynamic status and heart rhythm must be assessed, and a heart rhythm strip should be obtained.

Information on the balloon valvuloplasty, including number of inflations, should be documented in the source data and will be captured in the eCRFs.

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

11.7.3. Preparing and Using the Lotus Valve System

The Lotus 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 Boston Scientific personnel in accordance with the training plan before performing the procedure.

The Lotus Valve System must be prepared in accordance with the IFU.

Prior to insertion of the Lotus Valve catheter into the Lotus Introducer, the recommended target ACT of ≥250 seconds should be confirmed, with additional anticoagulant boluses (e.g., heparin) administered if needed.

The following summarizes the Lotus Valve System procedure.

1) The Lotus catheter is inserted in the Lotus Introducer and carefully advanced through the aorta and the aortic arch under fluoroscopy.
2) The catheter is then advanced slowly through the aortic annulus until the marker is appropriately positioned within the native aortic leaflets.
3) The valve is then deployed in the desired position.
4) Prior to the release of the Lotus Valve, assessment of its position and function is performed using contrast media 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 radiopaque marker as a guide.
6) Once repositioning is complete, the Lotus Valve is redeployed while maintaining the position of the marker.

7) Once the Lotus Valve position is deemed satisfactory, the release process is then initiated until the Lotus Valve is detached from the catheter.
8) The nosecone is then reseated on the catheter and the system is pulled back to the aorta and out of the body through the introducer.
9) A final post-deployment aortogram of the ascending aorta (including recommended rotational angiography of the valve frame) should be performed and forwarded to the Core Laboratory with the procedural cine-angiogram for analysis.
10) The Lotus Introducer is then removed.
11) The femoral access is then closed according to standard practice.

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

During the procedure, designated site 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
- Specifics of device type (such as size [23 mm vs. 27 mm] and model [if the Lotus Valve is not implanted])
- Time of first vascular puncture (femoral) and time of vascular closure (skin-to-skin time)
- Lotus Introducer insertion and removal time
- Descriptive information on balloon valve annuloplasty (e.g., size of balloon, number of balloon inflations)
- Any devices used and adjunctive procedures performed during implant procedure
- Heart rhythm after balloon valvuloplasty with rhythm strip
- Lotus Valve catheter insertion and removal time
- Descriptive information on Lotus Valve implantation procedure and information on valve repositioning (if performed)
- Adverse event (AE) assessment and associated treatment (including AE, serious adverse event [SAE], serious adverse device effect [SADE], unanticipated serious adverse device effect [USADE], adverse device effect [ADE] and Clinical Events Committee [CEC] events; see Section 21.
- Device deficiencies assessment (for the Lotus Valve System)

Note: All Lotus Valve implantation procedures will be performed with the support/presence of trained Boston Scientific personnel.

11.8. *Post-Procedure*

The following are to be performed post-procedure.

- Per society guidelines, antiplatelet therapy with aspirin and a thienopyridine is recommended to decrease the risk of thrombotic or thromboembolic complications if there are no contraindications to these medications[31]. Subjects must be treated with aspirin and clopidogrel for at least 1 month following valve implantation. If the study-specific dosages and durations for antiplatelet medications conflict with country-specific labeling for the medications, the country-specific labeling should take precedence.
    - After the Lotus Valve implant procedure, aspirin (recommended dose of ≥75 mg daily) must be given for at least 1 month. It is recommended that daily aspirin be given indefinitely thereafter as per local standard of care. Aspirin doses may be adjusted to the closest approximation based on local tablet formulation availability.
    - After the Lotus valve implant procedure, clopidogrel (recommended dose of 75 mg daily) is required for at least 1 month.
      Note: An alternative P2Y12 inhibitor (e.g., ticlopidine) may be prescribed as an alternative if subject is allergic to or intolerant of clopidogrel.
    - If the subject requires chronic anticoagulation (e.g., warfarin, dabigatran, etc.), either clopidogrel or aspirin is required in addition to the anticoagulant therapy post-procedure (but both aspirin and clopidogrel are not required).
- 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 at intervals per standard of care within 6-24 hours post-procedure.

11.9. *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 II eCRFs identify the specific data points to be collected.

- Physical examination including weight and height
- NYHA classification
- Neurological physical examination required in the main trial cohort, which must be performed by a neurologist or neurology fellow; assessors should be independent (not

involved with the care of study subjects; see Table 11.1-1). A neurological physical examination is not required in the extended trial cohort (see Table 11.1-2).

- NIHSS, which must be performed by certified personnel (external certification); assessors should be independent (not involved with the care of study subjects).
- Modified Rankin Scale score, which must be performed by certified personnel (external or internal certification); assessors should be independent (not involved with the care of study subjects).
- 12-lead ECG per the Core Laboratory guidelines (see study Manual of Operations) and must be forwarded for analysis.
- TTE, including assessment of effective orifice area, peak systolic and mean aortic valve gradient pressure, aortic regurgitation assessment, mitral regurgitation, LVEF, left ventricular end-diastolic and end-systolic diameter, TR jet velocity and LA volume, per the Echocardiography Core Laboratory procedure guidelines (see study Manual of Operations). All TTEs for enrolled subjects must be sent to the Echocardiography Core Laboratory for independent analyses.

  ***Note**:* 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.
- Current antiplatelet, anticoagulant (if applicable), and other cardiovascular medications
- Complete adverse event (AE, SAE, SADE, USADE, ADE, and CEC events) and device deficiencies assessment (with associated treatment)

11.10. *Follow-up*

All implanted subjects will be evaluated at 30 days, 3 months, 6 months, 12 months, 24 months, 36 months, 48 months, and 60 months post index procedure. Subjects who do not have the Lotus Valve implanted will be assessed through 30 days post procedure for safety/adverse events. Physical clinic visits or follow-up visits are scheduled for appointed times after the date of the procedure. It is important that this schedule be maintained as closely as possible for all subjects. Boston Scientific recognizes that subjects may not be able to return for all scheduled visits at precisely the date required, and therefore, a period of time in which each visit is allowed is indicated in Table 11.1-1. Studies not completed will be considered missed visits. 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 must be performed by study personnel; 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 (Table 26.2-1).

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.

11.10.1. 30-Day Follow-up (30±7 Days)

All enrolled subjects must be evaluated 30 days after the index procedure. During the 30-day follow-up, the following assessments must be completed. The REPRISE II eCRFs identify the specific data points to be collected.

- Physical examination including weight and height
- NYHA classification
- Modified Rankin Scale score, which must be performed by certified personnel (external or internal certification); assessors should be independent (not involved with the care of study subjects).
- Laboratory tests, including LDH and haptoglobin
- 12-lead ECG per the Core Laboratory guidelines (see study Manual of Operations) and must be forwarded to the Core Laboratory for analysis.
- Current antiplatelet, anticoagulant (if applicable), and other cardiovascular medications
- TTE including assessment of effective orifice area, peak systolic and mean aortic valve gradient pressure, aortic regurgitation assessment, mitral regurgitation, LVEF, left ventricular end-diastolic and end-systolic diameter, TR jet velocity and LA volume. TTE must be performed per the Echocardiography Core Laboratory procedure guidelines (see study Manual of Operations). All TTEs for enrolled subjects must be sent to the Echocardiography Core Laboratory for independent analyses.
- Quality of Life Surveys: SF-12 and EQ-5D Quality of Life Questionnaire
- Complete adverse event (AE, SAE, SADE, USADE, ADE, and CEC events) and device deficiencies assessment (with associated treatment)

11.10.2. 3-Month Follow-up (90±14 Days)

All implanted subjects must be evaluated 3 months after the index procedure. During the 3 month follow-up, the following assessments must be completed. The REPRISE II eCRFs identify the specific data points to be collected.

- Physical examination including weight and height
- NYHA classification
- Modified Rankin Scale score, which must be performed by certified personnel (external or internal certification); assessors should be independent (not involved with the care of study subjects).

- 12-lead ECG per the Core Laboratory guidelines (see study Manual of Operations) and must be forwarded for analysis.
- Current antiplatelet, anticoagulant (if applicable), and other cardiovascular medications
- TTE, including assessment of effective orifice area, peak systolic and mean aortic valve gradient pressure, aortic regurgitation assessment, mitral regurgitation, LVEF, left ventricular end-diastolic and end-systolic diameter, TR jet velocity and LA volume, per the Echocardiography Core Laboratory procedure guidelines (see study Manual of Operations). All TTEs for implanted subjects must be sent to the Echocardiography Core Laboratory for independent analyses.
- Complete adverse event (AE, SAE, SADE, USADE, ADE and CEC events) and device deficiencies assessment (with associated treatment)

11.10.3. 6-Month (180±30 Days) Follow-up

All implanted subjects must be evaluated at 6 months after the index procedure. During the 6-month follow-up, the following assessments must be completed. The REPRISE II eCRFs identify the specific data points to be collected.

- Physical examination including weight and height
- NYHA classification
- Modified Rankin Scale score, which must be performed by certified personnel (external or internal certification); assessors should be independent (not involved with the care of study subjects).
- 12-lead ECG per the Core Laboratory guidelines (see study Manual of Operations) and must be forwarded for analysis
- Current antiplatelet, anticoagulant (if applicable), and other cardiovascular medications
- TTE, including assessment of effective orifice area, peak systolic and mean aortic valve gradient pressure, aortic regurgitation assessment, mitral regurgitation, LVEF, left ventricular end-diastolic and end-systolic diameter, TR jet velocity and LA volume, per the Echocardiography Core Laboratory procedure guidelines (see study Manual of Operations). It must be sent to the Core Laboratory for independent analysis.
- Complete adverse event (AE, SAE, SADE, USADE, ADE and CEC events) and device deficiencies assessment (with associated treatment)
- Quality of Life Surveys: SF-12 and EQ-5D Quality of Life Questionnaires

11.10.4. 12-Month (365±45 Days) Follow-up

All implanted subjects must be evaluated at 12 months after the index procedure. During the 12-month follow-up, the following assessments must be completed. The REPRISE II eCRFs identify the specific data points to be collected.

- Physical examination including weight and height
- NYHA classification
- Modified Rankin Scale score, which must be performed by certified personnel (external or internal certification); assessors should be independent (not involved with the care of study subjects).
- Neurological physical examination required in the main trial cohort, which must be performed by a neurologist or neurology fellow (see Table 11.1-1); assessors should be independent (not involved with the care of study subjects). A neurological physical exam is not required in the extended trial cohort (see Table 11.1-2).
- NIHSS, which must be performed by certified personnel (external certification); assessors should be independent (not involved with the care of study subjects).
- Gait speed to walk 5 meters
- Rotational x-ray angiography to assess for structural valve frame integrity per the Imaging Core Laboratory procedure guidelines (see study Manual of Operations) is required in the main trial cohort. It must be forwarded to the Core Laboratory for analysis. Rotational x-ray angiography is not required in the extended trial cohort.
- 12-lead ECG per the Core Laboratory Guidelines (see study Manual of Operations) and must be forwarded for analysis
- Current antiplatelet, anticoagulant (if applicable), and other cardiovascular medications
- TTE, including assessment of effective orifice area, peak systolic and mean aortic valve gradient pressure, aortic regurgitation assessment, mitral regurgitation, LVEF, left ventricular end-diastolic and end-systolic diameter, TR jet velocity and LA volume, per the Echocardiography Core Laboratory procedure guidelines (see study Manual of Operations). It must be forwarded to the Core Laboratory for independent analysis.
- Complete adverse event (AE, SAE, SADE, USADE, ADE and CEC events) and device deficiencies assessment (with associated treatment)
- Quality of Life Surveys: SF-12 and EQ-5D Quality of Life Questionnaires

11.10.5. Annual Follow-up (±45 Days)

All enrolled subjects implanted with a Lotus Valve must be evaluated at 24, 36, 48, and 60 months after the index procedure. During the annual follow-up, the following assessments must be completed. The REPRISE II eCRFs identify the specific data points to be collected.

- Physical examination including weight and height
- NYHA classification
- Modified Rankin Scale score, which must be performed by certified personnel (external or internal certification); assessors should be independent (not involved with the care of study subjects).

- Current antiplatelet, anticoagulant (if applicable), and other cardiovascular medications
- TTE, including assessment of effective orifice area, peak systolic and mean aortic valve gradient pressure, aortic regurgitation assessment, mitral regurgitation, LVEF, left ventricular end-diastolic and end-systolic diameter, TR jet velocity, and LA volume, per the Echocardiography Core Laboratory procedure guidelines. All TTEs must be forwarded to the Core Laboratory for independent analyses.
- Rotational x-ray angiography to assess for structural valve frame integrity per the Imaging Core Laboratory procedure guidelines (see study Manual of Operations) is required in the main trial cohort. It must be forwarded to the Core Laboratory for analysis. If additional imaging is performed (e.g., cardiac CT or MRI scan), data may also be provided for analysis. Rotational x-ray angiography is not required in the extended trial cohort.
- Complete serious adverse event (SAE, SADE, USADE, and CEC events) and device deficiencies assessment (with associated treatment).
- Quality of Life Surveys: SF-12 and EQ-5D Quality of Life Questionnaires at 3 years and 5 years

11.10.6. Management of Missed or Late Visits

Missed or late visits will be recorded as protocol deviations and will be reviewed as such by the sponsor or designee on a regular basis in accordance with the applicable standard operating procedures.

11.10.7. Procedure for Determining when a Subject is 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 without due cause (after 30 days)
- 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
- A letter from the Investigator to Sponsor reporting subject as lost to follow up

11.10.8. Withdrawal and Replacement of Subjects

Subjects may withdraw from the study at any time, with or without reason and without prejudice to further treatment. Withdrawn subjects will not undergo any additional study follow-up, nor will they be replaced. The reason for withdrawal will be recorded (if given) in all cases of withdrawal. The investigator may discontinue a subject from participation in the study if the investigator feels that the subject can no longer fully comply with the requirements of the study or if any of the study procedures are deemed potentially harmful to

the subject. Data that have already been collected on withdrawn subjects will be retained and used for analysis but no new data will be collected after withdrawal.

11.10.9. Explant Procedure

If a Lotus Valve is explanted during conventional scheduled or emergent surgical valve replacement or during an autopsy, if possible, the explanted valve should be sent to an independent histopathology core laboratory 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.

11.11. *Study Completion*

All subjects will be evaluated at 30 days, 3 months, 6 months, 12 months, 24 months, 36 months, 48 months, and 60 months post index procedure. All visits are office visits. A subject's participation in the study will be considered complete after the 60-month visit.

11.12. *Source Documents*

It is preferable that original source documents (see Table 26.2-1 for definition) are maintained. Where copies of the original source document as well as printouts of original electronic source documents are retained, these should be signed and dated by a member of the investigation center team with a statement that it is a true reproduction of the original source document.

12. Statistical Considerations

12.1. *Endpoints*

12.1.1. Primary Endpoints

12.1.1.1. Primary Device Performance Endpoint

The study is powered to assess the primary device performance endpoint, which is the mean aortic valve pressure gradient at 30 days post implant as measured by TTE and assessed by an independent core laboratory. The null and alternative hypotheses for the primary device performance endpoint are as follows.

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

H_1: $Gradient_{30D} < PG$

where $Gradient_{30D}$ is the 30-day mean aortic valve pressure gradient for the Lotus Valve and PG is the performance goal (18 mm Hg).

Testing will be done for the primary device performance endpoint as described in the statistical analysis plan. A one-sample *t*-test will be used.

For the one-sample *t*-test, the test statistic is $t = \frac{\bar{x}_{30D} - PG}{s_{\bar{X}}}$,

where $\bar{x}_{30D}$ is the sample 30-day mean aortic valve pressure gradient,

PG is the performance goal,

$s_{\bar{x}} = \frac{1}{\sqrt{N}}\left(\sqrt{\frac{\sum(x - \bar{x}_{30D})^2}{N-1}}\right)$ is the sample standard error,

x is the 30-day mean aortic valve pressure gradient per subject, and

N is the sample size.

The degrees of freedom used in this test is $N-1$.

Two interim analyses will be conducted on the first 40 and 60 subjects and a final analysis will be conducted on the main trial cohort (N=120). The alpha-level for the interim and final analyses is adjusted using the Pocock alpha spending function method for unequal information time intervals[62]; they are 0.01123, 0.00792, and 0.01305, respectively. If the *P* value from the one-sample *t*-test is <alpha, the Lotus Valve will be concluded to have a 30-day mean aortic valve pressure gradient <18 mm Hg. This corresponds to the one-sided upper (1–alpha)% confidence bound of the observed 30-day mean aortic valve pressure gradient being <18 mm Hg.

A sensitivity analysis (tipping-point analysis) will be performed to assess the impact of subjects with inadequate follow-up (i.e., missing data) on the primary device performance endpoint and to assess the robustness of the conclusion of the primary analysis.

12.1.1.2. Sample Size – Primary Device Performance Endpoint

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

- Expected 30-day mean pressure gradient from Lotus Valve ≤ 15 mm Hg (based on the aforementioned literature review[23,32,34,44,46,63]
- Expected standard deviation = 7 mm Hg
- Performance goal (PG) = 18 mm Hg
- Test significance level (α) = 0.025 (1-sided)
- Power ($1 - \beta$) ≥ 80%
- Evaluable number of subjects = Minimum of 49 subjects
- Expected rate of attrition = 15% (9 subjects)

Given the above assumptions, the planned enrollment will be up to 120 subjects. Two planned interim analyses based on the primary device performance endpoint at 30 days post-implant procedure will be performed on the first 40 and 60 enrolled subjects. Enrollment of a total of 120 subjects is planned to meet regulatory requirements. A final analysis will be carried out on the fully enrolled main trial cohort.

12.1.1.3. Primary Safety Endpoint

Subsequent to the enrollment of the main trial cohort for device performance assessment (see Section 12.1.1.2), up to 130 more subjects will be enrolled in the extended trial cohort to perform a statistically powered assessment of the primary safety endpoint. The null and alternative hypotheses for the primary safety endpoint are as follows.

H_0: $\text{Mortality}_{30D} \geq PG$

H_1: $\text{Mortality}_{30D} < PG$

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

Testing will be done for the primary safety endpoint as described in the statistical analysis plan. A one-sample *z*-test will be used, the *z*-test statistic is $z = \frac{P_{30D} - PG}{s_p}$,

where

P_{30D} is the sample 30-day all-cause mortality rate,

PG is the performance goal,

$s_p = \sqrt{\frac{P_{30D}(1 - P_{30D})}{N}}$ is the sample standard error,

N is the sample size.

A sensitivity analysis (tipping-point analysis) will be performed to assess the impact of subjects with inadequate follow-up (i.e., missing data) on the primary safety endpoint and to assess the robustness of the conclusion of the primary analysis.

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

- Expected 30-day all-cause mortality rate = 9.8%
- Performance goal (PG) = 16 % (expected rate of 9.8% + testing margin of 6.2%)
- Test significance level (α) = 0.025 (1-sided)
- Power ($1 - \beta$) = 80%
- Expected rate of attrition = 2%

If the *P* value from the one-sample *z*-test is <0.025, it will be concluded that the primary safety endpoint for the Lotus Valve is less than the PG. This corresponds to the one-sided upper 97.5% confidence bound of the observed 30-day mortality rate being <16 %.

The expected rate of 9.8% for 30-day all-cause mortality is based on a literature review[8-13,16-18,20,22,24-28,32-37]. Given the above assumptions, 233 subjects will be required. In order to account for a 5% expected rate of attrition, a total of 250 subjects is required for the planned hypothesis testing.

12.1.1.4. Statistical Methods

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

12.1.2. Post-procedure Endpoints and Measurements

Post-procedure information will be collected at regularly scheduled follow-up examinations as detailed in the clinical study schedule (Table 11.1-1 and Table 11.1-2) 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. No inferences are planned on the additional endpoints and, therefore, alpha-adjustments for multiple comparisons will not be used. The Kaplan-Meier product-limit method will be used to determine rates for time-to-event endpoints. Adverse event and SAE rates will be reported.

12.2. *General Statistical Methods*

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

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

12.2.1. Analysis Sets

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

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

12.2.2. Control of Systematic Error/Bias

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

To control for inter-observer variability, an Echocardiography Core Laboratory will independently analyze echocardiography images collected for each subject during the study. Echocardiographic data obtained from the core laboratory will be used for analyses.

Similarly, an Electrocardiography Core Laboratory will independently analyze protocol-required 12-lead ECGs performed for each subject. Data obtained from the ECG core laboratory will be used for analyses.

12.3. *Data Analyses*

Baseline and outcome variables will be summarized using descriptive statistics for continuous variables (mean, standard deviation, number of observations, minimum and maximum) and discrete variables (percentage and count/sample). See Section 12.1.1 for a discussion on analysis of primary endpoints.

12.3.1. Other Endpoints/Measurements

Other endpoints not driven by statistical hypotheses are listed in Section 7.2 and Section 7.3.

12.3.2. Interim Analyses

12.3.3. There are 2 planned interim analyses for CE Mark dossier submission purposes. They will be based on the primary device performance endpoint at 30 days post-implant procedure and will be performed on the first 40 and 60 enrolled subjects. The final analysis of the primary device performance endpoint will be conducted on the fully enrolled main trial cohort (N=120). The Pocock alpha spending function method for unequal information time intervals[62] is used to adjust the alpha-level for each analysis: 0.01123, 0.00792, and 0.01305, respectively. Justification of Pooling

The analyses will be presented using data pooled across institutions as well as by center for the primary device performance endpoint and the primary safety endpoint.

Assessments of the poolability of subjects across centers will be made using the Chi-square test to determine if there is a relationship between the center and the primary safety endpoint,

and analysis of variance (ANOVA) to test for differences in the means of the primary device performance endpoint across centers. If the *P* value for the Chi-square test or ANOVA is ≥0.15, the data can be pooled across that center. In the analysis to justify pooling across centers, the centers with fewer than 5 subjects enrolled in the study will be combined into "virtual centers" based on geographic region so that "virtual centers" have ≥5 subjects in the study but no more than the largest enrolling center.

12.3.4. Multivariable Analyses

Univariate and multivariate analyses will be performed to assess the effect of potential predictors on the primary endpoint of mean aortic valve pressure gradient at 30 days post implant, as described in the statistical analysis plan.

12.3.5. Other Analyses

Exploratory univariate and multivariate analyses will be performed to assess the effect of potential predictors on the primary safety endpoint of all-cause mortality at 30 days post implant plus additional safety endpoints as described in the statistical analysis plan.

12.3.6. Changes to Planned Analyses

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

13. Data Management

13.1. *Data Collection, Processing, and Review*

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

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

13.3. *Core Laboratories*

13.3.1. Transthoracic Echocardiography (TTE) 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 Rotational X-Ray Angiography Core Laboratory

An independent Core Laboratory will centrally assess all of the CT and rotational X-ray 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. The screening CT Angiogram procedure guidelines and annual imaging acquisition protocol 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 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 to an independent histopathology laboratory for analyses.

14. Amendments

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. Appropriate approvals (e.g., IRB/EC/FDA/CA) of the revised protocol must be obtained prior to implementation.

15. 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/EC 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/EC, 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 notification, center re-training, or discontinuation) will be put into place by the sponsor.

16. Device Accountability

The Lotus Valve System and Lotus Introducer will be provided by the Sponsor to the clinical centers. This will occur only after the center has been initiated and all regulatory approvals as well as required documentation have been collected from the center.

The devices shall be securely maintained, controlled, and used only in this clinical study. Additionally, the study personnel must follow the instructions related to the storage of the

devices as noted in the IFU. Device Accountability Logs will be provided to the centers and will be used to track subjects and device allocations during the study.

The sponsor shall keep records to document the physical location of all investigational devices from shipment of investigational devices to the investigation centers until return or disposal.

Records shall be kept at each study center to document the physical location and conditions of storage of all investigational devices. Centers must not dispose of any devices for any reason at the center unless instructed to do so by Boston Scientific. Any device that is disposed of at the center must be recorded in the Device Accountability Log. The PI 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 and disposal of the investigational devices, which shall include the following; this will be verified by Boston Scientific personnel or its designee.

- Date of receipt
- Identification of each investigational device (Part/Reference and Lot numbers, 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 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 Boston Scientific that subject enrollment is complete, all unused devices must be returned to Boston Scientific or its designee. A copy of the Device Accountability Logs must also be provided to Boston Scientific.

17. Compliance

17.1. *Statement of Compliance*

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

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 investigational plan/protocol, ISO 14155, ethical principles that have their origins in the Declaration of Helsinki, any conditions of approval imposed by the reviewing IRB/EC, and prevailing local and/or country laws and/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 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 Valve training requirements as detailed in the REPRISE II Training Plan (see Section 17.4.1)
- 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 and observed device deficiency.
- Report to Boston Scientific, per the protocol requirements, all SAEs and device deficiencies that could have led to a SADE.
- Report to the IRB/EC and regulatory authorities any SAEs and device deficiencies that could have led to a SADE, if required by the national regulations or this protocol or by the IRB/EC, and supply Boston Scientific with any additional requested information related to the safety reporting of a particular event.
- Maintain the device accountability records and control of the 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 to perform monitoring and auditing activities, and be accessible to the monitor and respond to questions during monitoring visits.
- Allow and support regulatory authorities and the IRB/EC when performing auditing activities.
- Ensure that informed consent is obtained in accordance with this protocol and local IRB/EC 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 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.

17.2.1. Delegation of Responsibility

When specific tasks are delegated by an investigator, included but not limited to conducting the informed consent process, the investigator is responsible for providing appropriate training and adequate supervision of those to whom tasks are delegated. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

17.3. *Institutional Review Board/ Ethics Committee*

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

A copy of the written IRB/EC and/or competent authority approval of the protocol (or permission to conduct the study) and Informed Consent Form, must be received by the sponsor before recruitment of subjects into the study and shipment of investigational product/equipment. Prior approval must also be obtained for other materials related to subject recruitment or which will be provided to the subject.

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

17.4. *Sponsor Responsibilities*

All information and data sent to Boston Scientific and its authorized designee concerning subjects or their participation in this study will be considered confidential by Boston Scientific. Only authorized Boston Scientific personnel, representative or designee 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 Boston Scientific for the purposes of this study, publication, and to support future research and/or other business purposes. Data used in the analysis and reporting of this study will not be identified by specific subject name.

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. Boston Scientific Corporation may use subjects' health information to 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 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.

17.4.1. Training

The Sponsor is responsible for providing Investigators with the information and training they need to conduct the study properly and in accordance with the Training Plan. Study-specific training and education is required for all site staff with roles in this trial. The Sponsor is responsible for maintaining documentation of attendance at each of the training sessions provided.

In compliance with the initial requirements for training TAVR physicians in the latest Draft ISO 5840 Part 3 Annex O, Boston Scientific has developed a Training Plan that includes the following elements for implanting investigators.

- Review of subject selection and screening, with a detailed review of imaging requirements for implanting the device such as fluoroscopy, CT, and TTE
- Detailed description of all the Lotus Valve components
- Detailed description of the step-by step Lotus Valve procedure, with a complete review of the IFU including the indications for use, subject selection, contra-indications, precautions, warning, potential adverse events, pre-procedure set-up, sizing the valve, implant procedure, and post-procedure subject care
- Hands-on bench top demonstration of the valve and delivery system in a simulated model
- Use of the device in a simulation system
- A clinical training program for the proctors
- Cases review either via a taped case or library of previous cases, or by observing a Lotus Valve implantation
- The Training Phases will include the following.
    - **Phase I – Device Demonstration**: An initial introduction to the Lotus Valve device description and quick demonstration of the Step-by-Step Procedure using a simulation bench model ideally in the catheter lab, under fluoroscopy.
    - **Phase II – Online Training**: Following introduction to the device, the Operators (First and Second) as well as the site personnel who will be involved in the subject screening and selection will be given access to on-line training modules at the Lotus University training web-site. The online training includes modules that describe the subject selection process, the CRC roles and responsibilities, the device description and Step-by-Step procedure training.
    - **Phase III – Formal Training**: Hands-on (in-service) training using standard Lotus Valve components to practice the implantation procedure in a bench simulation model and/or a computer-based simulation (when available). During the bench model training, up to five procedures will be performed by the operators, initially guided by the Boston Scientific trainers (including Field Clinical Engineers [FCE]), with the last procedure being evaluated for the operators' certification.
    - **Phase IV – Refresher Training**: This training represents the last step of the hands-on training, with the purpose of providing more hands-on practice using the Lotus Valve System on the simulation bench model before the actual Lotus Valve implant procedures. Up to three practice procedures will be performed, with very minimal or no guidance from the Boston Scientific trainers in the catheter lab of the investigational site and under fluoroscopy. At the end of this training, the First and Second Operators will be provided with the official certification. TAVR investigators

with prior experience successfully implanting the Lotus Valve System may only need to complete this phase of the training plan.

- Case Observation: Prior to performing the first case, each investigator should be required to observe at least two Lotus Valve implantation procedures, performed by an experienced Lotus Valve implanter. The case observation may occur either via broadcasting, in the format of taped case, or in the catheter lab where the procedure is conducted, depending on the Operators and the administration of the center where the case is taking place.
- Proctoring: The investigator and co-investigators as well as the scrub team will be proctored by an experienced TAVR physician on a minimum of four Lotus Valve implantation procedures. These are to be performed in the investigator's institution with his 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.

17.4.2. Role of Boston Scientific Corporation Representatives

Boston Scientific personnel (including FCEs) will provide training and technical support to the investigator and other health care personnel (collectively HCP) as needed during implant and testing required by the protocol. Support may include addressing HCP questions or providing clarifications to HCPs concerning the operation of Boston Scientific equipment/devices. In addition, Boston Scientific 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.

17.5. *Insurance*

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

18. 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 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 Investigator continues to have sufficient staff and facilities to conduct the study safely and effectively. The Investigator/institution guarantees direct access to original source documents by Boston Scientific personnel, their designees, and appropriate regulatory authorities.

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

19. 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 and review of relevant literature, most recently from the Edwards Lifesciences' Placement of Aortic Transcatheter Valves (PARTNER) Trial[27,28].

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.

19.1. *Risks Associated with Transcatheter Aortic Valve Implantation Procedure and Lotus Valve System*

Adverse events (in alphabetical order) potentially associated with transcatheter aortic valve implantation as well as additional risks related to the use of the Lotus Valve System are listed below.

- Allergic reaction (including to medications, anesthesia, contrast, or device materials)
- Angina
- Arrhythmia or new conduction system injury (including need for pacemaker insertion)
- AV fistula
- Bleeding or hemorrhage
- Cardiac arrest
- Cerebrovascular accident, stroke or transient ischemic attack
- Coronary obstruction
- Death
- Device misplacement or migration
- Endocarditis
- Emboli (including air, tissue, thrombus or device materials)
- Fever
- Heart failure

- Hemolysis and/or hemolytic anemia
- Hematoma or lymphatic problems at the access sites
- Hemodynamic instability or shock
- Hypertension/hypotension
- Infection (local and/or systemic)
- Myocardial infarction
- Myocardial or valvular injury (including perforation or rupture)
- Neurologic deficits
- Pain
- Pericardial effusion or tamponade
- Pseudoaneurysm
- Renal insufficiency or failure
- Respiratory insufficiency or failure
- Valve dysfunction, deterioration or failure
- Valvular stenosis or regurgitation (central or paravalvular)
- Valve thrombosis
- Vessel injury (including spasm, trauma, dissection, perforation or rupture).

As a result of these complications, the subject may require medical, percutaneous or surgical intervention, including re-operation and replacement of the Lotus Valve. Such complications can be fatal.

As the Lotus valve 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.

19.2. *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 Boston Scientific 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 investigators who are experienced and skilled in TAVR and have completed training in the use of the Lotus Valve System.

- 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 22.1) and CEC (Section 22.1) adjudication of specified events as recommended by VARC[44].

In addition to its repositioning and self-centering features designed to facilitate optimal positioning, the Lotus Valve System provides physicians with control throughout the procedure by allowing them to pause, assess, lock, un-lock, incrementally reverse, resheath and, if needed, retrieve the valve prior to final release. The assessment of the need for such maneuvers is facilitated by early leaflet function during valve deployment. These features allow the physician to place the valve correctly at the first attempt, the capacity to reposition the device if the initial deployment is considered to be suboptimal, and the capability of retrieving 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 anti-platelet therapy is recommended to minimize any risk of thrombus formation, stroke, or transient ischemic attack (TIA). Neurological assessments will be performed at each required follow-up visit to identify any change in the neurological status of the subjects as recommended by VARC[44,48].

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 Boston Scientific. Qualified employees of Boston Scientific, 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.

19.3. *Anticipated Benefits*

19.3.1. Potential Benefits to the TAVR Procedure

Transcatheter aortic valve replacement (TAVR) may offer certain advantages when compared to surgical replacement of the stenotic native aortic valve, particularly in high risk subjects. Known benefits associated with TAVR, as described in the scientific literature (see summary in Section 4 of this document and details in Sections 2 and 3 of the investigator 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
- Opportunity to receive a new aortic prosthesis in spite of having been refused surgery or being of high surgical risk profile

19.3.2. Potential Benefit Using the Lotus Valve System

Potential benefits that may be associated specifically with use of the Lotus™ 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 or obviated need for valve-in-valve repeat intervention
- Reduced incidence of paravalvular aortic regurgitation due to the Adaptive Seal

19.4. *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 predicate Sadra Medical TAVR products. When used according to the IFU, all known risks associated with the TAVR procedure and the specific use of the Lotus 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.

20. Informed Consent

Subject participation in this clinical study is voluntary. Informed Consent is required from all subjects or their legally authorized representative. The Investigator is responsible for ensuring that Informed Consent is obtained 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: 2011and the ICH guidelines for GCP; any applicable national regulations; and local Ethics Committee and/or Regulatory authority body, as applicable. The ICF must be approved by the center's IRB/EC, or central IRB, if applicable.

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

The process of obtaining Informed Consent shall:

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

21. Safety Reporting

21.1. *Definitions and Classification*

Adverse event definitions are provided in Table 21.1-1.

Table 21.1-1: Adverse Event Definitions

Term	Definition[a]
Adverse Event (AE) *Ref: ISO 14155:2011*	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 1**: This definition includes events related to the investigational medical device or the comparator. **Note 2**: This definition includes events related to the procedures involved. **Note 3**: For users or other persons, this definition is restricted to events related to investigational medical devices.
Adverse Device Effect (ADE) *Ref: ISO 14155:2011*	Adverse event related to the use of an investigational medical device **Note 1**: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. **Note 2**: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.
Serious Adverse Event (SAE) *Ref: ISO 14155:2011*	Adverse event that: • Led to a death • Led to serious deterioration in the health of the subject, that either resulted in: o a life-threatening illness or injury, or

Table 21.1-1: Adverse Event Definitions

Term	Definition[a]
	○ a permanent impairment of a body structure or a body function, or ○ in-patient or prolonged hospitalization, or ○ medical or surgical intervention to prevent life- threatening illness or injury or permanent impairment to a body structure or a body function, • Led to foetal distress, foetal 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 14155:2011*	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated Serious Adverse Device Effect (USADE) *Ref: ISO 14155:2011*	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report **Note**: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.
Device Deficiency *Ref: ISO 14155:2011* *Ref: MEDDEV 2.7/3 12/2010*	A device deficiency is any inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. **Note 1**: Device deficiencies include malfunctions, use errors, and inadequate labeling. **Note 2**: All device deficiencies that could have led to a SADE if a) suitable action had not been taken or b) if intervention had not been made or c) if circumstances had been less fortunate shall be reported as required by the local IRB/EC, national regulations, or the protocol.

a: Other definitions may apply per local reporting requirements.

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 a specific SAE (see Table 21.1-1 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.

Any AE experienced by the study subject beginning from the time of Lotus Introducer sheath insertion, whether during or subsequent to the procedure, must be recorded in the eCRF.

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

Based on the VARC[44,48] recommendations and definitions, the adverse events and/or safety endpoints requiring adjudication by the CEC include but are not limited to the following.

- Mortality: all-cause, cardiovascular, and non-cardiovascular
- Neurologic event: disabling or non-disabling stroke, and TIAs
- Myocardial infarction (MI): periprocedural (≤72 hours post index procedure) and spontaneous (>72 hours post index procedure)
- Bleeding events: life-threatening (or disabling), major and minor
- Acute kidney injury (≤7 days post index procedure): based on AKIN System[49,50] Stage 3 (including renal replacement therapy), Stage 2, and Stage 1
- Vascular complications: major and minor
- Repeat procedure for valve-related dysfunction (surgical or interventional therapy)
- Hospitalization for valve-related symptoms or worsening congestive heart failure (NYHA class III or IV)
- New permanent pacemaker implantation resulting from new or worsened conduction disturbances (including new left bundle branch block [LBBB] and third degree atrioventricular block)
- New onset of atrial fibrillation or atrial flutter
- Coronary obstruction (periprocedural)
- Ventricular septal perforation (periprocedural)
- Mitral apparatus damage (periprocedural)
- Cardiac tamponade (periprocedural)
- Prosthetic aortic valve malapposition, including valve migration, valve embolization, ectopic valve deployment, or transcatheter aortic valve (TAV)-in-TAV deployment
- Prosthetic aortic valve thrombosis
- Prosthetic aortic valve endocarditis

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 26.2-1).

21.2. *Relationship to Study Device(s)*

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

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

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

21.3. *Investigator Reporting Requirements*

The communication requirements for reporting to Boston Scientific are as shown in Table 21.3-1.

Table 21.3-1: Investigator Reporting Requirements

Event Classification	Communication Method	Communication Timeline
Unanticipated Serious Adverse Device Effect (USADE)	Complete AE 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 Lotus Introducer sheath insertion for all subjects • Terminating at the end of the study
	Provide copies of all relevant source documents requested by Boston Scientific	• As soon as possible after reporting the event
Serious Adverse Event (SAE) including Serious Adverse Device Effects (SADE)	Complete AE eCRF page with all available new and updated information	• Within 2 business days of first becoming aware of the event or as per local/regional regulations. • Beginning from time of Lotus Introducer sheath insertion for all subjects • Reporting required through the end of the study
	Provide all relevant source documentation (unidentified) for reported event	• When documentation is available
Adverse Event (AE)	Complete AE eCRF page, which contains such information as date of AE, treatment of AE resolution, assessment of seriousness and relationship to the device	• Review with CRA during next monitoring visit • Beginning from time of Lotus Introducer sheath insertion for all subjects • Reporting required through

Table 21.3-1: Investigator Reporting Requirements

Event Classification	Communication Method	Communication Timeline
		12 months
Device Deficiencies, Failures, Malfunctions, and Product Nonconformities	Complete applicable CRF fields/pages with all available new and updated information.	• Within 1 business day of first becoming aware of the event and as per local/regional regulations • Beginning from time of Lotus Introducer sheath insertion for all subjects • Reporting required through the end of the study

Abbreviations: AE=adverse event; CRA=clinical research associate; eCRF=electronic case report form; SADE=serious adverse device effect; SAE=serious adverse event' USADE=unanticipated serious adverse device effect

21.4. *Boston Scientific Device Deficiencies*

All Lotus Valve System device deficiencies (including but not limited to failures, malfunctions, use errors, product nonconformities, and labeling errors) must be documented on the appropriate eCRF and, if possible, the device should be returned to Boston Scientific 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 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 21.3-1.

21.5. *Reporting to Regulatory Authorities / IRBs / ECs / Investigators*

Boston Scientific Corporation will notify all participating study centers if SAEs/SADEs/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 AE information to all participating investigators and regulatory authorities as applicable according to local reporting requirements.

The PI is responsible for informing the IRB/EC, and regulatory authorities of 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/IEC must be provided to Boston Scientific in accordance with local requirements.

22. Committees

22.1. *Safety Monitoring Process*

To promote early detection of safety issues, the CEC and 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 Boston Scientific's Global Safety Office, which is responsible for coordinating the collection of information for the subject dossier from the centers and core laboratories. During regularly scheduled monitoring visits, clinical research monitors will support the dynamic reporting process through their review of source document information.

22.1.1. Clinical Events Committee

A 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 sites, and adjudicate study endpoint related clinical events. The responsibilities, qualifications, membership, and committee procedures of the CEC are outlined in the CEC charter.

22.1.2. Data Monitoring Committee

The 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 Boston Scientific. 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.

22.2. *Case Review Committee*

A CRC will be comprised of interventional cardiologists and cardiac surgeons, including the Study PI, Country PIs, other investigators, Proctors and Medical Consultants experienced in TAVR for their clinical/medical expertise; and the Sponsor for technical expertise on the Lotus Valve System requirements. This committee will be responsible for the review of

subject screening data to confirm eligibility given the high surgical risk subject population being studied and to ensure consistency of subjects enrolled across study sites.

22.3. *Steering Committee*

A Steering Committee consisting of Sponsor Clinical Management, the Study Coordinating PI, Lead Country PIs, 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.

23. Suspension or Termination

23.1 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/ECs, and regulatory authorities, as applicable, will be notified in writing in the event of study termination.

23.1.1 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 Boston Scientific to suspend or discontinue development of the device.

23.2 Termination of Study Participation by the Investigator or Withdrawal of IRB/EC Approval

Any investigator or IRB/EC in the REPRISE II study may discontinue participation in the study or withdrawal approval of the study, respectively, with suitable written notice to Boston Scientific. Investigators, associated IRBs/ECs, and regulatory authorities, as applicable, will be notified in writing in the event of these occurrences.

23.3 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 Boston Scientific. The IRB/EC 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/EC terminates participation in the study, participating investigators, associated IRBs/ECs, and regulatory authorities, as applicable, will be notified in writing. Detailed information on how enrolled subjects will be managed thereafter will be provided by Boston Scientific.

In the event an investigator terminates participation in the study, study responsibility will be transferred to a co-investigator, if possible. In the event there are no opportunities to transfer investigator responsibility; detailed information on how enrolled subjects will be managed thereafter will be provided by Boston Scientific. The investigator must return all documents and investigational product to Boston Scientific, unless this action would jeopardize the rights, safety, or welfare of the subjects.

23.4 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 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 investigator participation, all study devices and testing equipment, as applicable, will be returned to Boston Scientific unless this action would jeopardize the rights, safety or well-being of the subjects. The IRB/EC and regulatory authorities, as applicable, should 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 Boston Scientific notifies the investigational center otherwise.

24. Publication Policy

In accordance with the Corporate Policy on the Conduct of Human Subject Research, Boston Scientific requires disclosure of its involvement as a sponsor or financial supporter in any publication or presentation relating to a Boston Scientific study or its results. In accordance with the Corporate Policy for the Conduct of Human Subject Research, Boston Scientific 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, Boston Scientific 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.
- Boston Scientific involvement in the publication preparation and the Boston Scientific 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.

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26. Abbreviations and Definitions

26.1. *Abbreviations*

Abbreviations are shown in Table 26.1-1.

Table 26.1-1: Abbreviations and Acronyms

Abbreviation/Acronym	Definition
ACT	activated clotting time
ADE	adverse device effect
AE	adverse event
AKIN	Acute Kidney Injury Network
AO	ascending aorta
AR	aortic regurgitation
AS	aortic stenosis
AV	Atrioventricular
AVA	aortic valve area
AVR	aortic valve replacement
BARC	Bleeding Academic Research Consortium
BMI	body mass index
CBC	complete blood count
CPB	cardiopulmonary bypass
CRA	clinical research associate

Table 26.1-1: Abbreviations and Acronyms

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

Table 26.1-1: Abbreviations and Acronyms

Abbreviation/Acronym	Definition
TEE	transesophageal Doppler echocardiography
TIA	transient ischemic attack
TR	tricuspid regurgitation
TTE	transthoracic Doppler echocardiography
USADE	unanticipated serious adverse device effect
URL	upper reference limit (defined as 99th percentile of normal reference range)
VARC	Valve Academic Research Consortium

26.2. *Definitions*

Terms are defined in Table 26.2-1. See Table 26.1-1for abbreviations.

Table 26.2-1: Definitions

Term	Definition
ACUTE KIDNEY INJURY (AKI) (AKIN System[49,50])	Change in serum creatinine (up to 7 days) compared to baseline: • Stage 1: Increase in serum creatinine to 150–199% (1.5–1.99 × increase compared with baseline) OR increase of ≥0.3 mg/dl (≥26.4 mmol/L) • Stage 2: Increase in serum creatinine to 200–299% (2.0–2.99 × increase compared with baseline) • Stage 3: Increase in serum creatinine to ≥300% (>3 × increase compared with baseline) OR serum creatinine of ≥4.0 mg/dL (≥354 mmol/L) with an acute increase of at least 0.5 mg/dL (44 mmol/L) -OR- Based on urine output (up to 7 days): • Stage 1: <0.5 ml/kg per hour for >6 but <12 hours • Stage 2: <0.5 ml/kg per hour for >12 but <24 hours • Stage 3: <0.3 ml/kg per hour for ≥24 hours or anuria for ≥12 hours Note 1: Subjects receiving renal replacement therapy are considered to meet Stage 3 criteria irrespective of other criteria.
ACUTE VESSEL OCCLUSION	The state of complete luminal obstruction with no antegrade blood flow
ADVERSE EVENT (AE)	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 1: This definition includes events related to the investigational medical device or the comparator. Note 2: This definition includes events related to the procedures involved. Note 3: For users or other persons, this definition is restricted to events related to investigational medical devices.
ADVERSE DEVICE EFFECT (ADE)	Adverse event related to the use of an investigational medical device Note 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. Note 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

Table 26.2-1: Definitions

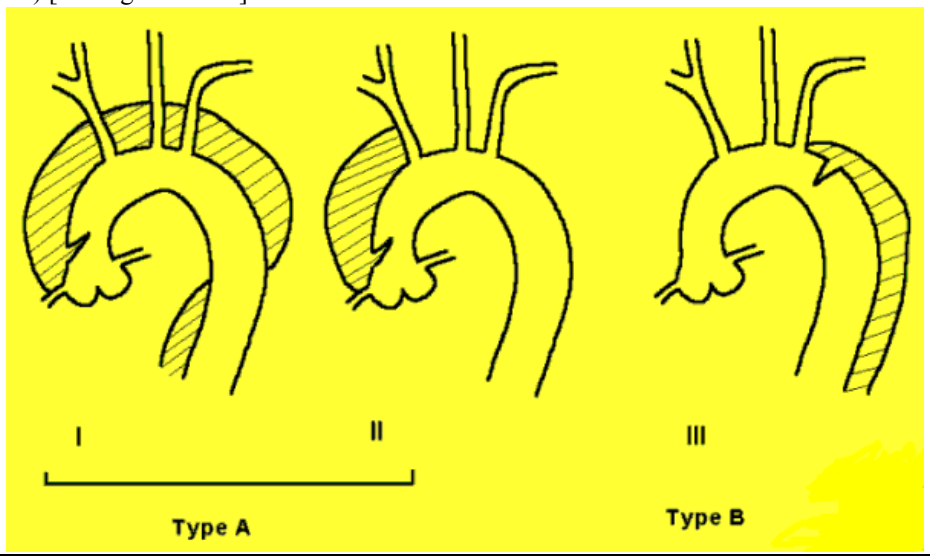
Term	Definition
AORTIC DISSECTION	Intimal tear resulting in blood splitting the aortic media and producing a false lumen that can progress in an antegrade or retrograde direction Aortic dissection is further classified using Stanford classification (Types A and B depending on whether ascending or descending aorta involved) or DeBakey classification (Types I, II and III) [see Figure below]. 
AORTIC REGURGITATION (AR)	The leaking of the aortic valve that causes blood to flow in the reverse direction during ventricular diastole, from the aorta into the left ventricle. The echocardiographic findings in severe aortic regurgitation include the following. • An AR color jet dimension >60% of the left ventricular outflow tract diameter (may not be true if the jet is eccentric) • The pressure half-time of the regurgitant jet is <250 msec • Early termination of the mitral inflow (due to increase in LV pressure due to the AR) • Early diastolic flow reversal in the descending aorta. • Regurgitant volume >60 mL • Regurgitant fraction >55%
ARRHYTHMIA	Any variation from the normal rhythm of the heartbeat, including sinus arrhythmia, premature beat, heart block, atrial fibrillation, atrial flutter and tachycardia. Complete heart block, ventricular tachycardia and ventricular fibrillation are considered major arrhythmias. Data should be collected on any new arrhythmia resulting in hemodynamic instability or requiring therapy (therapy includes electrical/medical cardioversion or initiation of a new medication [oral anticoagulation, rhythm or rate controlling therapy]). New onset atrial fibrillation or atrial flutter (AF) is diagnosed as any arrhythmia within hospitalization that has the ECG characteristics of AF and lasts sufficiently long to be recorded on a 12-lead ECG, or at least 30 seconds on a rhythm strip. The therapeutic approach to new-onset AF (spontaneous conversion, electrical or medical cardioversion, initiation of oral anticoagulation, and rate or rhythm control medications) and any clinical consequences should be documented. Note: See also definitions for conductance disturbance and permanent pacemaker.
BLEEDING[44,48]	Life-threatening or Disabling Bleeding

Table 26.2-1: Definitions

Term	Definition
	• Fatal bleeding (Bleeding Academic Research Consortium [BARC] type 5[64,65]) • Bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome (BARC type 3b and 3c) • Bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery (BARC type 3b) • Overt source of bleeding with drop in hemoglobin of ≥5 g/dL or whole blood or packed red blood cells (RBC) transfusion ≥4 units (BARC type 3b)* <u>Major Bleeding (BARC type 3a)</u> • Overt bleeding either associated with a drop in the hemoglobin level of at least 3.0g/dL or requiring transfusion of 2 or 3 units of whole blood/RBC, or causing hospitalization or permanent injury, or requiring surgery AND does not meet criteria of life-threatening or disabling bleeding <u>Minor Bleeding (BARC type 2 or 3a, depending on the severity)</u> • Any bleeding worthy of clinical mention (e.g., access site hematoma) that does not qualify as life-threatening, disabling, or major * Given one unit of packed RBC typically will raise blood hemoglobin concentration by 1 g/dL, an estimated decrease in hemoglobin will be calculated.
CARDIAC DECOMPENSATION	Inability of the heart to maintain adequate circulation
CARDIAC TAMPONADE	Evidence of a new pericardial effusion associated with hemodynamic instability and clearly related to the TAVR procedure. Clinical syndrome caused by the accumulation of fluid in the pericardial space, resulting in reduced ventricular filling and subsequent hemodynamic compromise.
CARDIOGENIC SHOCK	An insufficient forward cardiac output to maintain adequate perfusion of vital organs to meet ongoing demands for oxygenation and metabolism. Cardiogenic shock is due to either inadequate left ventricular pump function (such as in congestive heart failure) or inadequate left ventricular filling (such as in cardiac tamponade). Cardiogenic shock is defined as sustained hypotension (>30 minutes) with evidence of tissue hypoperfusion including oliguria (<30 mL/h), cool extremities, cyanosis, and altered mental status.
CEREBRAL INFARCTION	Evidence of brain cell death from imaging studies or pathological examination. If there are clinical symptoms, then it is a stroke; otherwise, it is an asymptomatic cerebral infarction.
CHRONIC RENAL INSUFFICIENCY	Subject has chronic impairment of kidney function.
CONDUCTION DISTURBANCES	Implant-related new or worsened cardiac conduction disturbances include new or worsened first degree atrioventricular (AV) block, second degree AV block (Mobitz I or Mobitz II), third degree AV block, incomplete right bundle branch block (RBBB), RBBB, intraventricular conduction delay, left bundle branch block (LBBB), left anterior fascicular block, or left posterior fascicular block, including block requiring permanent pacemaker implant <u>Note 1</u>: High grade AV block is considered persistent if it is present every time the underlying rhythm is checked. <u>Note 2</u>: See also definitions for arrhythmia and permanent pacemaker.
CONVERSION TO OPEN SURGERY	Conversion to open sternotomy during the TAVR procedure secondary to any procedure-related complications

Table 26.2-1: 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.
DEATH	<u>All-cause Death</u> Death from any cause after a valve intervention. <u>Cardiovascular Death</u> Any one of the following criteria is met. • Any death due to proximate cardiac cause (e.g., myocardial infarction, cardiac tamponade, worsening heart failure) • Sudden or unwitnessed death • Death of unknown cause • Death caused by noncoronary vascular conditions such as neurological events, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular disease • All procedure-related deaths, including those related to a complication of the procedure or treatment for a complication of the procedure • All valve-related deaths including structural or nonstructural valve dysfunction or other valve-related adverse events <u>Non-cardiovascular Death</u> • Any death in which the primary cause of death is clearly related to another condition (e.g. trauma, cancer, suicide)
DEVICE DEFICIENCY	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. <u>Note 1</u>: Device deficiencies include malfunctions, use errors, and inadequate labeling.
DEVICE FAILURE	A device failure is identified whenever the criteria for device success are not met.

Table 26.2-1: Definitions

Term	Definition
DEVICE MIGRATION	Device migration is defined as an upward or downward displacement of the implanted valve from its original implant location, after initial correct positioning within the aortic annulus from its initial position, with or without consequences. This can be confirmed by X-ray, echocardiography, CT scan or MRI or valve migration demonstrated by direct assessment during open heart surgery or at autopsy.
DEVICE RELATED COMPLICATIONS	Complications associated with the device as it relates to delivery, placement, efficacy or durability; these may involve the implanted device or the delivery system.
DEVICE SUCCESS	Device Success as defined by VARC post-implant procedure. VARC 1 [44] • Successful vascular access, delivery and deployment of the device and successful retrieval of the delivery system • Correct position of the device in the proper anatomical location • Intended performance of the prosthetic heart valve (aortic valve area >1.2 cm^2 and mean aortic valve gradient <20 mmHg or peak velocity <3 m/s, without moderate or severe prosthetic valve aortic regurgitation) • Only one valve implanted in the proper anatomical location VARC 2 [48] • Absence of procedural mortality • Correct positioning of a single transcatheter valve into the proper anatomical location • Intended performance of the Lotus Valve (indexed effective orifice area >0.85 cm^2/m^2 [>0.7 cm^2/m^2 for BMI ≥30 kg/ m^2] plus either a mean aortic valve gradient <20 mm Hg or a peak velocity <3m/sec, without moderate or severe prosthetic valve aortic regurgitation)
ECTOPIC VALVE DEPLOYMENT	Permanent deployment of the valve prosthesis in a location other than the aortic root.
EMBOLISM	Examples include a free flowing blood clot or lesion material that is located in the systemic or pulmonary circulation. Embolism may be manifested by a neurological event or a noncerebral embolic event.
ENCEPHALOPATHY	Altered mental state (e.g., seizures, delirium, confusion, hallucinations, dementia, coma, psychiatric episode, etc.)
ENDOCARDITIS	**Infective endocarditis** is diagnosed based on Duke criteria[66] and necessitates the following. • Two major criteria -OR- • One major and three minor criteria -OR- • Five minor criteria Major Criteria • Positive blood culture for infective endocarditis o Typical microorganism consistent with infective endocarditis from 2 separate blood cultures, as noted below. ▪ Viridans streptococci, *Streptococcus bovis*, or HACEK group (*Haemophilus* [*Haemophilus parainfluenzae, Haemophilus aphrophilus, and Haemophilus paraphrophilus*], *Actinobacillus actinomycetemcomitans* [*Aggregatibacter actinomycetemcomitans*], *Cardiobacterium hominis, Eikenella corrodens, Kingella kingae* -OR- ▪ Community-acquired *Staphylococcus aureus* or enterococci, in the absence of

Table 26.2-1: Definitions

Term	Definition
	a primary focus -OR- o Microorganisms consistent with infective endocarditis from persistently positive blood cultures defined as noted below. ▪ Two (2) positive cultures of blood samples drawn >12 hours apart -OR- ▪ All of 3 or a majority of 4 separate cultures of blood (with first and last sample drawn 1 hour apart) • Evidence of endocardial involvement o Positive echocardiogram for infective endocarditis defined as noted below. ▪ Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation -OR- ▪ Abscess -OR- ▪ New partial dehiscence of prosthetic valve -OR- o New valvular regurgitation (worsening or changing of preexisting murmur not sufficient) <u>Minor Criteria</u> • Predisposition: predisposing heart condition or intravenous drug use • Fever: temperature >38.0° C (100.4° F) • Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway lesions • Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth spots, and rheumatoid factor • Microbiological evidence: positive blood culture but does not meet a major criterion as noted above or serological evidence of active infection with organism consistent with infective endocarditis • Echocardiographic findings: consistent with infective endocarditis but do not meet a major criterion as noted above **Implanted valve endocarditis** includes any infection involving an implanted valve. The diagnosis of operated valvular endocarditis is based on one of the following criteria. • Fulfillment of the Duke endocarditis criteria as defined above • Evidence of abscess, paravalvular leak, pus, or vegetation confirmed as secondary to infection by histological or bacteriologic studies during a re-operation • Findings of abscess, pus, or vegetation involving a repaired or replaced valve during an autopsy.
EXPLANT	Removal of the investigational valve implant for any reason.
FRAILTY	Slowness, weakness, exhaustion, wasting and malnutrition, poor endurance and inactivity, loss of independence.
HEMOLYSIS	Two plasma free hemoglobin values >40 mg/dL with the two readings taken within a single 48-hour period. If the second plasma free hemoglobin assessment is not performed within 48 hours following an initial determination of >40 mg/dL, this would qualify as an AE.
HOSTILE CHEST	Any of the following or other reasons that make redo operation through sternotomy or right anterior thoracotomy prohibitively hazardous:

Table 26.2-1: Definitions

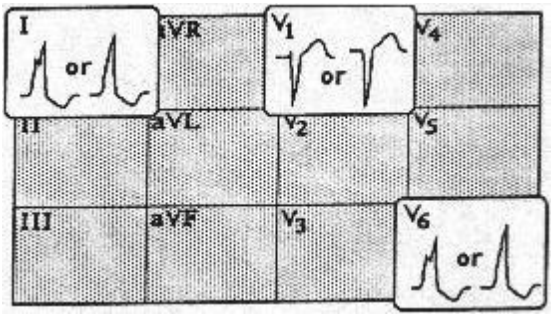
Term	Definition
	• Abnormal chest wall anatomy due to severe kyphoscoliosis or other skeletal abnormalities (including thoracoplasty, Potts' disease) • Complications from prior surgery • Evidence of severe radiation damage (e.g. skin burns, bone destruction, muscle loss, lung fibrosis or esophageal stricture) • History of multiple recurrent pleural effusions causing internal adhesions
INTERNAL MAMMARY ARTERY OR OTHER CRITICAL CONDUIT(S) CROSSING MIDLINE AND/OR ADHERENT TO POSTERIOR TABLE OF STERNUM	A patent IMA graft that is adherent to the sternum such that injuring it during reoperation is likely. A patient may be considered extreme risk if any of the following are present: • The conduit(s) are radiographically indistinguishable from the posterior table of the sternum. • The conduit(s) are radiographically distinguishable from the posterior table of the sternum but lie within 2-3mm of the posterior table.
INTRACRANIAL HEMORRHAGE	Collection of blood between the brain and skull; subcategorized as epidural, subdural, and subarachnoid bleeds.
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	**Periprocedural MI (≤72 hours after the index procedure)**

Table 26.2-1: Definitions

<table>
<tr><th>Term</th><th>Definition</th></tr>
<tr><td>INFARCTION (MI)</td><td>
• 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
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[67].
</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</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</td></tr>
</table>

Table 26.2-1: Definitions

Term	Definition
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
PARAVALVULAR REGURGITATION	Leakage due to a separation of the prosthetic valve from the annulus. Any evidence of leakage of blood around the device. Diagnosis of paravalvular regurgitation may be obtained from TEE/TTE, however, definitive diagnosis is obtained at re-operation, explant, or autopsy.
PERMANENT PACEMAKER (PPM) IMPLANTATION	Implantation of new PPM after the index procedure resulting from new or worsened conduction disturbances (including new left bundle branch block [LBBB] and third degree atrioventricular block) • Procedure-related: PPM is implanted in subjects with new onset or worsened conduction disturbances occurring post index procedure • Not related to procedure: PPM is implanted in subjects with known conduction disturbances that did not advance after the index procedure. Note: See also definitions for arrhythmia and conductance disturbance.
PORCELAIN AORTA	Heavy circumferential calcification of the entire ascending aorta extending to the arch such that aortic cross-clamping is not feasible
PROCEDURE RELATED COMPLICATIONS	Complications associated with any part of the vascular access procedure, associated treatments or necessary secondary interventions that do not necessarily involve the device. This includes morbidity associated with either pre-medication, or anesthesia, or other adjunct to the surgical procedure. Other technical errors including inappropriate subject selection, inappropriate operator techniques, measurements, or judgment that do not involve the device itself are also included.
PROCEDURE-RELATED EVENTS	Events occurring during or as a direct result of the index procedure.
REPEAT PROCEDURE FOR VALVE-RELATED DYSFUNCTION	Any surgical or percutaneous interventional catheter procedure that repairs, otherwise alters or adjusts, or replaces a previously implanted valve. In addition to surgical re-operations, enzymatic, balloon dilatation, interventional manipulation, repositioning, or retrieval, and other catheter-based interventions for valve-related complications are also considered reinterventions. Cardiac reinterventions will be categorized as repeat TAVR, valvuloplasty, or surgical AVR. • Conversion to open surgery • Conversion to open sternotomy during the TAVR procedure secondary to any procedure-related complications. • Unplanned use of CPB • Unplanned use of CPB for hemodynamic support at any time during the TAVR

Table 26.2-1: Definitions

Term	Definition
	procedure.
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.
SERIOUS ADVERSE EVENT (SAE)	Adverse event that resulted in the following. • Led to a death • Led to serious deterioration in the health of the subject, that resulted in one or more of the following. o Life-threatening illness or injury o Permanent impairment of a body structure or a body function o In-patient or prolonged hospitalization o Medical or surgical intervention to prevent life- threatening illness or injury or permanent impairment to a body structure or a body function, • Led to fetal distress, fetal death or a congenital abnormality or birth defect Note 1: 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)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event
SOURCE DATA (per ISO 14155:2011)	All information in original records of clinical findings, observations, or other activities in a clinical investigation, necessary for the reconstruction and evaluation of the clinical investigation
SOURCE DOCUMENT (per ISO 14155:2011)	Printed, optical or electronic document containing source data. Examples: Hospital records, laboratory notes, device accountability records, photograhic negatives, radiographs, records kept at the investigation center, at the laboratories and at the medico-technical departments involvced in the clinical investigation.
STROKE[44,48]	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.

Table 26.2-1: Definitions

Term	Definition
	• Hemorrhagic Stroke is defined as an acute episode of focal or global cerebral or spinal dysfunction caused by an intraparenchymal, intraventricular, or subarachnoid hemorrhage Note 1: The CEC will adjudicate ischemic versus hemorrhagic stroke. Note 2: A stroke may be classified as undetermined if there is insufficient information to allow categorization as ischemic or hemorrhagic **Stroke Diagnostic Criteria** • Rapid onset of a focal or global neurological deficit with at least one of the following: change in level of consciousness, hemiplegia, hemiparesis, numbness or sensory loss affecting one side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke • Duration of a focal or global neurological deficit ≥24 h; OR <24 h, if available neuroimaging documents a new hemorrhage or infarct; OR the neurological deficit results in death • No other readily identifiable nonstroke cause for the clinical presentation (e.g., brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences), to be determined by or in conjunction with designated neurologist • Confirmation of the diagnosis by at least one of the following. o Neurology or neurosurgical specialist o Neuroimaging procedure (MRI or CT scan), but stroke may be diagnosed on clinical grounds alone Note 3: Subjects with non-focal global encephalopathy will not be reported as a stroke without unequivocal evidence based upon neuroimaging studies (CT scan or brain MRI). **Stroke Definitions** Diagnosis as above, preferably with positive neuroimaging study • Non-disabling: Modified Rankin Scale (mRS) score <2 at 90 days OR one that does not result in an increase of at least one mRS category from an individual's pre-stroke baseline • Disabling: Modified Rankin Scale score ≥2 at 90 days AND an increase of at least one mRS category from an individual's pre-stroke baseline Note 4: Modified Rankin Scale assessments should be made by qualified individuals according to a certification process. Note 5: Assessment of the mRS score should occur at all scheduled visits in a study; mRS also should be performed after a stroke and at 90 days after the onset of any stroke.
STRUCTURAL VALVE DETERIORATION	Component of time-related valve safety defined as follows. • Valve-related dysfunction: Mean aortic valve gradient ≥20 mmHg, EOA ≤0.9-1.1 cm^2, and/or DVI <0.35 AND/OR moderate or severe prosthetic valve regurgitation (per VARC definition) • Requiring repeat procedure (TAVR or SAVR).
TAV-IN-TAV DEPLOYMENT	An additional valve prosthesis is implanted within a previously implanted prosthesis because of suboptimal device position and/or function during or after the index procedure.
TRANSIENT ISCHEMIC ATTACK (TIA)	• Transient episode of focal neurological dysfunction caused by brain, spinal cord, or retinal ischemia, without acute infarction • Duration of a focal or global neurological deficit is <24 h

Table 26.2-1: Definitions

Term	Definition
	• Neuroimaging does not demonstrate a new hemorrhage or infarct (if performed) Note: The difference between TIA and ischemic stroke is the presence of tissue damage or new sensory-motor deficit persisting >24 hours. By definition, TIA does not produce lasting disability.
UNANTICIPATED SERIOUS ADVERSE DEVICE EFFECT (USADE)	Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report Note: An anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity, or outcome has been identified in the risk analysis report.
UNPLANNED USE OF CPB	Unplanned use of cardiopulmonary bypass (CPB) for hemodynamic support at any time during the TAVR procedure
VALVE EMBOLIZATION	The valve prosthesis moves during or after deployment such that it loses contact with the aortic annulus.
VALVE MALAPPOSITION	Includes valve migration, valve embolization, ectopic valve deployment, or transcatheter aortic valve (TAV)-in-TAV deployment.
VALVE MIGRATION	After initial correct positioning the valve prosthesis moves upward or downward within the aortic annulus from its initial position, with or without consequences (e.g., regurgitation).
VALVE-RELATED DYSFUNCTION	Mean aortic valve gradient ≥20 mmHg, EOA ≤0.9-1.1 cm^2, and/or DVI <0.35 AND/OR moderate or severe prosthetic valve aortic regurgitation (per VARC definition)
VALVE-RELATED SYMPTOMS/CHF REQUIRING HOSPITALIZATION	The need for hospitalization associated with valve-related symptoms or worsening CHF (NYHA Class III or IV) is intended to serve as a basis for calculation of a "days alive outside the hospital" endpoint. Included are heart failure, angina, or syncope due to aortic valve disease requiring intervention or intensified medical management; clinical symptoms of CHF with objective signs including pulmonary edema, hypoperfusion, or documented volume overload AND administration of intravenous diuresis or inotropic therapy, performance of aortic valvuloplasty, institution of mechanical support (intra-aortic balloon pump or ventilation for pulmonary edema), or hemodialysis for volume overload; clear documentation of anginal symptoms AND no clinical evidence that angina was related to coronary artery disease or acute coronary syndrome; documented loss of consciousness not related to seizure or tachyarrhythmia.
VALVE THROMBOSIS	Any thrombus attached to or near an implanted valve that occludes part of the blood flow path, interferes with valve function, or is sufficiently large to warrant treatment. Note that valve-associated thrombus identified at autopsy in a patient whose cause of death was not valve-related or at operation for an unrelated indication should not be reported as valve thrombosis.
VASCULAR ACCESS SITE AND ACCESS RELATED COMPLICATIONS	**Major Vascular Complications** • Any aortic dissection, aortic rupture, annulus rupture, left ventricle perforation, or new apical aneurysm/pseudoaneurysm • Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, hematoma, irreversible nerve injury, compartment syndrome, percutaneous closure device failure*) ***leading to*** death, life-threatening or major bleeding**, visceral ischaemia, or neurological impairment • Distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage • The use of unplanned endovascular or surgical intervention ***associated*** with death,

Table 26.2-1: Definitions

Term	Definition
	major bleeding, visceral ischaemia or neurological impairment • Any new ipsilateral lower extremity ischemia documented by patient symptoms, physical exam, and/or decreased or absent blood flow on lower extremity angiogram • Surgery for access site-related nerve injury • Permanent access site-related nerve injury **Minor Vascular Complications** • Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysms , hematomas, percutaneous closure device failure*) not leading to death, life-threatening or major bleeding**, visceral ischaemia or neurological impairment • Distal embolization treated with embolectomy and/or thrombectomy and not resulting in amputation or irreversible end-organ damage • Any unplanned endovascular stenting or unplanned surgical intervention not meeting the criteria for a major vascular complication • Vascular repair or the need for vascular repair (via surgery, ultrasound-guided compression, transcatheter embolization, or stent-graft) ***Percutaneous Closure Device Failure** Failure of a closure device to achieve hemostasis at the arteriotomy site leading to alternative treatment (other than manual compression or adjunctive endovascular ballooning) Note 1**:** Pre-planned surgical access or a planned endovascular approach to vascular closure (e.g., "pre-closure")[68,69] should be considered as part of the TAVR procedure and not as a complication, unless untoward clinical consequences are documented (e.g., bleeding complications, limb ischemia, distal embolization, or neurological impairment). Note 2: If unplanned percutaneous or surgical intervention does not lead to adverse outcomes this is not considered a major vascular complication. ** Refers to VARC bleeding definitions[44]
VENTRICULAR SEPTAL PERFORATION	Angiographic or echocardiographic evidence of a new septal perforation during or after the TAVR procedure
VESSEL PERFORATION	Unexpected puncture of the vessel with evidence of extravasation into extraluminal surrounding tissue or space requiring treatment using interventional or surgical techniques

Abbreviations: ADE=adverse device effect; AE=adverse event; AR=aortic regurgitation; AVA=aortic valve area; AVR= aortic valve replacement; CEC= Clinical Events Committee; CK= creatine kinase; CT=computed tomography; DVI=Doppler velocity index; ECG=electrocardiogram; EOA=effective orifice area; FEV= forced expiratory volume; LBBB=left bundle branch block; LV= left ventricle; MI=myocardial infarction; MRI=magnetic resonance imaging; NYHA=New York Heart Association; PPM=permanent pacemaker; RBC=red blood cell; SADE=serious adverse device effect; SAE=serious adverse event; TAVR =transcatheter aortic valve replacement; TEE=transesophageal Doppler echocardiography; TIA=transient ischemic attack; USADE= unanticipated serious adverse device effect; URL=upper reference limit (defined as 99th percentile of normal reference range); VARC=Valve Academic Research Consortium

27. Appendices

27.1. *Changes in Protocol Versions*

27.1.1. Protocol Version AA to Version AB

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

27.1.2. Protocol Version AB to Version AC

Table 27.1-2 lists changes between protocol versions AB and AC.

27.1.3. Protocol Version AC to Version AD

Table 27.1-3 lists changes between protocol versions AC and AD.

27.1.4. Protocol Version AD to Version AE

Table 27.1-4 lists changes between protocol versions AD and AE.

27.1.5. Protocol Version AE to Version AF

Table 27.1-5 lists changes between protocol versions AE and AF.

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

<table>
<tr><th>Section Modified</th><th>Text as Written in REPRISE II Protocol Version AA</th><th>Text as Written in REPRISE II Protocol Version AB</th><th>Justification for Modification</th></tr>
<tr><td>Page 2</td><td>Original Release: 05-June-2012</td><td>Current Version: 07-August-2012
Revision History
<table><tr><th>Revision Number</th><th>Release Date</th><th>Reason for Change</th></tr><tr><td>AB</td><td>07-Aug-2012</td><td>See Appendix 1</td></tr></table></td><td>Protocol updated based on VARC 2 manuscript specifications</td></tr>
<tr><td rowspan="8">2. Protocol Synopsis
Additional Measurements</td><td>Additional measurements based on the VARC[a,b] endpoints and definitions (see Table 17.2-1 in the Appendix for definitions)…</td><td>Additional measurements based on the VARC[a,b] endpoints and definitions (see Table 26.2-1for definitions)…</td><td>Corrected table number</td></tr>
<tr><td>Mortality: all-cause, cardiovascular, and procedure-related</td><td>Mortality: all-cause, cardiovascular, and non-cardiovascular</td><td rowspan="5">Updated per VARC-2 manuscript</td></tr>
<tr><td>Composite of all-cause mortality and stroke</td><td>Composite of all-cause mortality and disabling stroke</td></tr>
<tr><td>Acute kidney injury (≤72 hours post index procedure): based on the modified RIFLE Stage 3…</td><td>Acute kidney injury (≤72 hours post index procedure): based on the AKIN System Stage 3…</td></tr>
<tr><td>Failure of current therapy for aortic stenosis: requiring hospitalization for valve-related symptoms or worsening congestive heart failure, NYHA class III or IV</td><td>Hospitalization for valve-related symptoms or worsening congestive heart failure (NYHA class III or IV)</td></tr>
<tr><td>New permanent pacemaker implantation resulting from new conduction…</td><td>New permanent pacemaker implantation resulting from new or worsened conduction…</td></tr>
<tr><td>Functional status as evaluated by the New York Heart Association (NYHA) classification and Modified Rankin Scale</td><td>• Functional status as evaluated by the following:
o 5-m gait speed test (at 1 year compared to baseline)
o New York Heart Association (NYHA) classification and Modified Rankin Scale
• Neurological status as determined by the following:
o National Institutes of Health Stroke Scale (NIHSS) at discharge and 1 year
o Modified Rankin Scale (mRS)</td><td>Updated per VARC-2 manuscript and for clarity</td></tr>
<tr><td>Note 1: … all-cause mortality, disabling stroke, life-threatening/disabling bleeding, acute kidney injury Stage 3 (including renal replacement therapy), periprocedural MI, major …</td><td>Note 1: … all-cause mortality, all stroke, life-threatening bleeding, acute kidney injury Stage 2 or 3 (including renal replacement therapy), coronary artery obstruction requiring intervention, major …</td><td>Updated per VARC-2 manuscript</td></tr>
</table>

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

Section Modified	Text as Written in REPRISE II Protocol Version AA	Text as Written in REPRISE II Protocol Version AB	Justification for Modification
	Note 2: … mortality (after 30 days); disabling stroke; failure … prosthetic heart valve dysfunction (indexed effective orifice area <0.85 cm^2,/m^2 [≤0.7 cm^2/m^2 for BMI ≥30 kg/m^2] and either a mean aortic valve gradient ≥20 mm Hg or a peak velocity ≥3m/sec, OR moderate or severe prosthetic valve aortic regurgitation).	***Note 2:*** … mortality (after 30 days); all stroke; failure … prosthetic heart valve dysfunction (mean aortic valve gradient ≥20 mm Hg, effective orifice area ≤0.9-1.1 cm^2, and/or Doppler velocity index (DVI) <0.35 AND/OR moderate or severe prosthetic valve aortic regurgitation [per VARC definition]).	
	Note 3: ... bleeding (unless clearly unrelated to valve therapy).	***Note 3:*** ... bleeding (unless clearly unrelated to valve therapy based on investigator assessment). ***Note 4:*** For subjects diagnosed with a neurological event (e.g., stroke, transient ischemic attack), a neurological physical exam, NIHSS assessment, and mRS must be performed after the event; mRS must also be administered at 90 days post-neurological event.	
	a: Serruys P, *et al.* (2012) VARC Clinical Research Updates: Important Changes from VARC-2. Transcatheter Valve Therapeutics, Seattle, USA.	a: Serruys P, *et al.* (2012) VARC Clinical Research Updates: Important Changes from VARC-2. Transcatheter Valve Therapeutics, Seattle, USA (manuscript pending publication).	
2. Protocol Synopsis Adjunctive Pharmacologic Therapy	Anticoagulant therapy (e.g., unfractionated heparin) per local standard of care must be administered prior to the implant…	Anticoagulant therapy (e.g., unfractionated heparin) per local standard of care must be administered during the implant…	Per TAVR guideline recommendations
	Aspirin The loading dose... implant procedure. Clopidogrel The loading dose... implant procedure. c: Holmes, D. R., et al. J Am Coll Cardiol. 2012;59:1200	Aspirin The loading dose… implant procedure or immediately after. Clopidogrel[d] The loading dose... implant procedure or immediately after c: Holmes, D. R., et al. J Am Coll Cardiol. 2012;59:1200 d: An alternative P2Y12 inhibitor may be prescribed if subject is allergic to or intolerant of clopidogrel.	Updated for clarity and to allow use of alternative P2Y12 inhibitors
2. Protocol Synopsis Exclusion Criteria	EC 11. …either aspirin or clopidogrel/ticlopidine.	EC 11. …either aspirin or clopidogrel[d] d: An alternative P2Y12 inhibitor may be prescribed if subject is allergic to or intolerant of clopidogrel.	
3. Table of Contents	Table of Contents - 8.3 Justification for the Study Design	Table of Contents - 8.3Study Design Justification - Section 27. Appendices	Updated for clarity: Sections 4.2 and 8.3 had the same title Updated to reflect

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

Section Modified	Text as Written in REPRISE II Protocol Version AA	Text as Written in REPRISE II Protocol Version AB	Justification for Modification
			addition of appendix with table of changes.
4.1 Justification…	Table 4.1-1 references Table 4.1-1 MACCE column Table 4.1-1 Title	Table 4.1-1 updated with additional references Table 4.1-1: replaced MACCE column with "Vascular Complications" column Table 4.1-1 Title: Removed "MACCE"	Added newer references Use of individual measurements rather than the composite MACCE to better compare across studies
5.1.1 Lotus valve	The maximum height of both valve sizes in the deployed state is 19 mm.	The frame height of both valve sizes in the deployed state is approximately 19 mm.	Updated for clarity
7.3 Additional Measurements	Additional measurements … and Table 17.2-1 in the Appendix for definitions…	Additional measurements … and Table 26.2-1 in the Appendix for definitions…	Corrected table number
	Mortality: all-cause, cardiovascular, and procedure-related	Mortality: all-cause, cardiovascular, and non-cardiovascular	Updated per VARC-2 manuscript
	Composite of all-cause mortality and stroke	Composite of all-cause mortality and disabling stroke	
	Acute kidney injury (≤72 hours post index procedure): based on the modified RIFLE Stage…	Acute kidney injury (≤72 hours post index procedure): based on the AKIN System Stage…	
	Failure of current therapy for aortic stenosis: requiring hospitalizations for valve-related symptoms or worsening congestive heart failure NYHA class III or IV	Hospitalization for valve-related symptoms or worsening congestive heart failure (NYHA class III or IV)	
	New permanent pacemaker implantation resulting from new conduction…	New permanent pacemaker implantation resulting from new or worsened conduction…	
	Functional status as evaluated by the New York Heart Association (NYHA) classification and Modified Rankin Scale	• Functional status as evaluated by the following: o 5-m gait speed test[35] (at 1 year compared to baseline) o New York Heart Association (NYHA) classification • Neurological status as determined by the following: o National Institutes of Health Stroke Scale (NIHSS) at discharge and 1 year o Modified Rankin Scale (mRS)	Updated per VARC-2 manuscript and to add clarity

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

Section Modified	Text as Written in REPRISE II Protocol Version AA	Text as Written in REPRISE II Protocol Version AB	Justification for Modification
	Note 1: The VARC safety composite at 30 days (including all-cause mortality, disabling stroke, life-threatening/disabling bleeding, acute kidney injury, peri-procedural MI, major vascular complication, and repeat procedure for valve-related dysfunction) will be reported.	***Note 1:*** The VARC safety composite at 30 days will be reported. This includes all-cause mortality, all stroke, life-threatening bleeding, acute kidney injury Stage 2 or 3, coronary artery obstruction requiring intervention, major vascular complication, and repeat procedure for valve-related dysfunction.	
	Note 2: The VARC efficacy composite at 1 year (including all-cause mortality [after 30 days], disabling stroke, failure of current therapy for aortic stenosis [requiring hospitalizations for valve-related symptoms or worsening congestive heart failure, NYHA class III or IV], and prosthetic heart valve dysfunction [indexed effective orifice area <0.85 cm^2/m^2 (≤0.7 cm^2/m^2 for BMI≥30 kg/m^2) and either a mean aortic valve gradient ≥20 mm Hg or a peak velocity ≥3m/sec, OR moderate or severe prosthetic valve aortic regurgitation]) will be reported.	***Note 2:*** The VARC efficacy composite at 1 year will be reported. This includes all-cause mortality (after 30 days), all stroke, requiring hospitalizations for valve-related symptoms or worsening congestive heart failure (NYHA class III or IV), and prosthetic heart valve dysfunction (mean aortic valve gradient ≥20 mm Hg, effective orifice area ≤0.9-1.1 cm2 and/or Doppler velocity index [DVI] <0.35, AND/OR moderate or severe prosthetic valve aortic regurgitation [per VARC definition])	
	Note 3: ... bleeding (unless clearly unrelated to valve therapy).	***Note 3:***... bleeding (unless clearly unrelated to valve therapy based on investigator assessment). ***Note 4:*** For subjects diagnosed with a neurological event (e.g., stroke, transient ischemic attack), a neurological physical exam, NIHSS assessment, and mRS must be performed after the event; mRS must also be administered at 90 days post-neurological event. ***Note 5:*** The VARC clinical efficacy composite includes the need for hospitalization associated with valve-related symptoms or worsening congestive heart failure (CHF) as a basis for calculation of a "days alive outside the hospital" endpoint. This includes 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	

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

Section Modified	Text as Written in REPRISE II Protocol Version AA	Text as Written in REPRISE II Protocol Version AB	Justification for Modification
		related to seizure or tachyarrhythmia.	
8.3. Justification	8.3 Justification for the Study Design In order to support the stated objectives of this study (see Section 4) while also limiting… In addition to the risk-benefit analysis noted above (see Section 4.0), ongoing…	8.3 Study Design Justification In order to support the stated objectives of this study (see Section 6) while also limiting… In addition to the risk-benefit analysis noted in Section 4.2 (see also Section 19), ongoing…	Updated for clarity
9.3 Exclusion Criteria	EC 11. Subject … or clopidogrel/ticlopidine (subjects … or clopidogrel/ticlopidine). EC17. Subject has untreated clinically significant coronary artery disease EC24. Subject has a preexisting conduction system…	EC 11. Subject … or clopidogrel (subjects … or clopidogrel).* EC17. Subject has untreated coronary artery disease, which in the opinion of the treating physician, is clinically significant and requires requiring revascularization. EC24. Subject has a preexisting untreated conduction system… * An alternative P2Y12 inhibitor may be prescribed if subject is allergic to or intolerant of clopidogrel.	Updated for clarity and to allow use of alternative P2Y12 inhibitors
11. Study Methods	Figure 11.1-1 REPRISE Study Design	Figure 11.1-1 REPRISE Study Design Updated figure to add symbols for Gait Speed assessment at 1 year and post-deployment aortogram	Updated for clarity and/or per VARC 2 manuscript
11. Study Methods Table 11.1-1	Table 11.1-1 Study Event Schedule	Table 11.1-1 Study Event Schedule Added row for post-deployment aortogram and "X" in "procedure" column Added "X" in 12-Month column for gait speed	
	a: No later than 10 days prior to the index procedure(unless otherwise specified)	a: It is recommended that screening occur no later than 10 days prior to the index procedure (unless otherwise specified); results from these assessments should be submitted to the CRC at least 10 days prior to the planned procedure to allow for adequate scheduling of subject review at a CRC meeting.	
	c: … Visits should be an office/clinical visit…	c: … Visits must be an office/clinical visit…	
	e: Neurological … For subjects diagnosed with any neurological event (stroke, transient ischemic attack, and encephalopathy), a neurological physical exam and NIHSS should also be performed. mRS must also be administered at 30 and 90 days post-neurological event.	e: Neurological … For subjects diagnosed with a neurological event (e.g., stroke, transient ischemic attack), a neurological physical exam, mRS and NIHSS should also be performed; mRS must also be administered at 90 days post-neurological event.	

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

Section Modified	Text as Written in REPRISE II Protocol Version AA	Text as Written in REPRISE II Protocol Version AB	Justification for Modification
	f: … Heart rhythm strip should be obtained…	f: … Heart rhythm strip must be obtained…	
	i: Frailty… and comorbidity (Charlson Index).	i: Frailty… and comorbidity (Charlson Index); at 1 year, gait speed to walk 5 meters must be assessed again.	
	o: Annual imaging… frame integrity. If additional …; data should be provided for analysis.	o: Annual imaging… frame integrity must be performed. If additional…; data may be provided for analysis.	
	r: Final post-deployment aortogram of the ascending aorta should be performed and sent to the CT Core Laboratory.	r: final post-deployment aortogram of the ascending aorta should be performed and sent to the CT Core Laboratory. Note that with the addition of this line there is a change in the subsequent footnote labeling: "r" becomes "s" and "s" becomes "t." Added abbreviation information for AKI, CRC, and mRS	
	t: Device deficiencies, SAEs…	t: Device deficiencies (for the Lotus Valve System), SAEs…	
	j: Transthoracic… guidelines (see study Manual of Operations). If TTE image quality is suboptimal, transesophageal Doppler echocardiography (TEE) may be substituted.	j: Transthoracic… guidelines (see study Manual of Operations).	TEE will not provide all data needed for comparisons with TTE data.
	g: Laboratory tests at baseline include CBC, platelet count, LDH, haptoglobin, serum creatinine, cardiac enzymes, and international normalized ratio if subject is on warfarin.	g: Laboratory tests at baseline include CBC, platelet count, LDH, haptoglobin, serum creatinine, and cardiac enzymes. …. Acute kidney injury (AKI) should be assessed through discharge/7 days based on the AKIN system.	Removed because INR assessment is standard of care. Added reference to AKI per VARC 2 manuscript
11.4 Screening Assessments	Specific data points will be collected… o A CT angiogram … aortic root dimensions for device sizing. It must be performed … measurements and analyses... o Either a CT or invasive angiogram ... o Figure 11.4 1 shows … valve size (e.g., aortic annulus diameter of 23–24mm).	Sites will be trained on the screening process as detailed in the REPRISE II Training Plan (see Section 17.4.1). Specific data points will be collected… o A CT angiogram … aortic root dimensions to determine eligibility and device sizing. It must be performed … measurements and independent analyses... o Either a CT or invasive angiogram … for independent measurements and review by the CRC to confirm subject's eligibility. o Figure 11.4 1 shows … valve size.	Revised for clarity.

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

Section Modified	Text as Written in REPRISE II Protocol Version AA	Text as Written in REPRISE II Protocol Version AB	Justification for Modification
	Physical examination including weight and height (body mass index), and NYHA classification	o Physical examination including weight and height o NYHA classification	Revised for clarity. Sites do not have to provide BMI.
	…for independent analyses. If TTE image quality is suboptimal, transesophageal Doppler echocardiography (TEE) may be substituted.	…for independent analyses.	TEE will not provide all data needed for comparisons with TTE data.
11.5 Baseline Assessments	• Neurological physical examination, which must be performed by a neurologist or neurology fellow independent of the study • NIH Stroke Scale (NIHSS), which must be performed by certified personnel (external certification) independent of the study •Modified Rankin Score, which must be performed by certified personnel (external or internal certification) independent of the study	• Neurological physical examination, which must be performed by a neurologist or neurology fellow; assessors should be independent of the study • NIH Stroke Scale (NIHSS), which must be performed by certified personnel (external certification); assessors should be independent of the study • Modified Rankin Scale score, which must be performed by certified personnel (external or internal certification); assessors should be independent of the study	Revised for clarity. Note that similar changes are made in Sections 11.9, 11.10.1, 11.10.2, 11.10.3, 11.10.4, and 11.10.5
	Laboratory Tests - International normalized ratio (INR) if subject is on warfarin	Laboratory Tests	Removed because INR assessment is standard of care.
11.6 Preprocedure Medications	• Antiplatelet therapy … <u>Aspirin</u> A loading dose … prior to the implant procedure... <u>Clopidogrel</u> A loading dose … prior to the implant procedure. Ticlopidine can be prescribed as an alternative if subject is allergic or intolerant to clopidogrel. • Anticoagulant therapy … care prior to the implant procedure…	• Antiplatelet therapy … <u>Aspirin</u> A loading dose… prior to the implant procedure or immediately after… <u>Clopidogrel</u> A loading dose … prior to the implant procedure or immediately after. **Note 1**: An alternative P2Y12 inhibitor can be prescribed as an alternative if subject is allergic to or intolerant of clopidogrel. • Anticoagulant therapy … care during the implant procedure…	Updated for clarity and to allow use of alternative P2Y12 inhibitors.
11.7.2 Valvuloplasty	Information on the balloon valvuloplasty, including number of inflations, will be recorded in the eCRFs.	Information on the balloon valvuloplasty, including number of inflations, should be documented in the source data and will be captured in the eCRFs.	Updated for clarity

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

Section Modified	Text as Written in REPRISE II Protocol Version AA	Text as Written in REPRISE II Protocol Version AB	Justification for Modification
11.7.3 Preparing and Using the Lotus Valve System	The following summarizes the Lotus Valve System procedure... 9) A final post-deployment aortogram of the ascending aorta should be performed. The following information will be collected during the procedure. • Descriptive information on balloon valve annuloplasty … • Heart rhythm after balloon valvuloplasty… • Adverse event (AE) assessment (including … • Device deficiencies assessment	The following summarizes the Lotus Valve System procedure… 9) A final post-deployment aortogram of the ascending aorta should be performed and forwarded to the Core Laboratory for analysis. The following information will be collected during the procedure. • Descriptive information on balloon valve annuloplasty … • Any devices used and adjunctive procedures performed during implant procedure • Heart rhythm after balloon valvuloplasty with rhythm strip… • Adverse event (AE) assessment and associated treatment (including … • Device deficiencies assessment (for the Lotus Valve System)	
11.8 Post-Procedure	• After the Lotus valve implant procedure, aspirin …must be given… • After the Lotus valve implant procedure, clopidogrel is required… Ticlopidine can be prescribed as an alternative if subject is allergic to or intolerant of clopidogrel.	After the Lotus valve implant procedure, aspirin …should be given… After the Lotus valve implant procedure, clopidogrel is recommended ... **Note:** An alternative P2Y12 inhibitor (e.g. ticlopidine) can be prescribed as an alternative if subject is allergic to or intolerant of clopidogrel.	Updated for clarity and to allow use of alternative P2Y12 inhibitors
11.9 Prior to Discharge…	…based on the assessments below. • Complete adverse … device deficiencies assessment	…based on the assessments below. The REPRISE II eCRFs identify the specific data points to be collected. • Physical examination including weight and height • Complete adverse … device deficiencies assessment (with associated treatment)	Updated for clarity. Note that similar changes are made in Sections 11.10.1, 11.10.2, 11.10.3, 11.10.4, 11.10.5 See also changes made in Section 11.5.

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

Section Modified	Text as Written in REPRISE II Protocol Version AA	Text as Written in REPRISE II Protocol Version AB	Justification for Modification
11.9 and 11.10 Follow-up 11.10.1, 11.10.2, 11.10.3, 11.10.4, 11.10.5	TTE… independent analyses. If TTE image quality is suboptimal, transesophageal Doppler echocardiography (TEE) may be substituted.	TTE… independent analyses.	Data are acquired using TTE; TEE will not provide all data needed for comparisons
11.10 Follow-up	Each follow-up visit … personnel and data … will be recorded in the eCRFs.	Each follow-up visit … personnel; data …will be recorded in source documentation and captured in the eCRFs.	Revised for clarity
11.10.4 12-Month		- Gait speed to walk 5 meters	Added per VARC-2 manuscript
11.10.5 Annual Follow-up	- Complete adverse event (AE, SAE, SADE, …deficiencies assessment	- Complete serious adverse event (SAE, SADE, …deficiencies assessment (with associated treatment)	Adverse events are not collected beyond 12 months.
11.10.7 Procedure…	• Documentation of … next of kin, including one that confirms the subject is lost to follow-up	• Documentation of … next of kin	Revised for clarity.
11.10.9 Explant Procedure	If a Lotus 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 to an independent histopathology core laboratory for macroscopic and microscopic analyses. Information on the explant procedure must be documented in the Explant Form of the eCRFs.	If a Lotus Valve is explanted during conventional scheduled or emergent surgical valve replacement or during an autopsy, if possible, the explanted valve should be sent to an independent histopathology core laboratory 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.	
11.12 Source Documents	Where copies… are retained, these shall be signed…	It is preferable that original source documents (see Table 26.2-1for definition) are maintained. Where copies… are retained, these should be signed…	
12.1.1.2 Sample Size	…and 60 enrolled subjects. Enrollment of the additional 60 subjects is planned…	…and 60 enrolled subjects. Enrollment of a total of 120 subjects is planned…	
12.2.1 Analysis Sets	…The primary safety endpoint will be evaluated along with additional endpoints and measurements on an ITT basis…	…The primary safety endpoint will be evaluated on an ITT basis…	

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

Section Modified	Text as Written in REPRISE II Protocol Version AA	Text as Written in REPRISE II Protocol Version AB	Justification for Modification
13.3.2 CT and Rotational…	An independent Core Laboratory will centrally assess all of the CT and rotational X-ray data in this study. These analyses…	An independent Core Laboratory will centrally assess all of the CT and rotational X-ray data in this study to reduce variability. These analyses…	
16 Device Accountability	The principal investigator … shall keep records … which shall include the following.	The principal investigator … shall keep records … which shall include the following; this will be verified by BSC personnel.	
17.4 Sponsor Responsibilities	All data used in the analysis and reporting of this study will be without identifiable reference to specific subject name.	Data used in the analysis and reporting of this study will not be identified by specific subject name.	
17.4.1 Training	The Sponsor is responsible for providing Investigators with the information and training they need to conduct the study properly and in accordance with the Clinical Protocol and Training Plan.	The Sponsor is responsible for providing Investigators with the information and training they need to conduct the study properly and in accordance with the Training Plan.	
21.1 Definitions and Classification	• Mortality: all-cause, cardiovascular, and procedure-related • Acute kidney injury (≤72 hours post index procedure): based on modified RIFLE… • Failure of current therapy for aortic stenosis: requiring hospitalization for valve-related symptoms or worsening congestive heart failure, NYHA class III or IV • New permanent pacemaker implantation resulting from new conduction…	• Mortality: all-cause, cardiovascular, and non-cardiovascular • Acute kidney injury (≤72 hours post index procedure): based on AKIN System… • 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…	Updated per VARC-2 manuscript
21.4 Boston Scientific Device Deficiencies	All Lotus Valve System device deficiencies … should be documented on the appropriate eCRF…. …If an AE results from a device deficiency or other device issue, the AE should be reported on the appropriate eCRF. Device deficiencies that did not lead to an AE but … fortunate should be reported as described in Table 21.3-1.	All Lotus Valve System device deficiencies … must be documented 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 … fortunate must be reported as described in Table 21.3-1.	Revised for clarity
25. Bibliography		Updated to include the additional references added to Table 4.1-1	Newer references
26.1 Abbreviations		Updated to includes additional abbreviations and remove some not used	Revised for clarity
Table 26.2-1 Definitions	ACUTE KIDNEY INJURY (Modified RIFLE Classification) — • Stage 1: … to 150–199% (1.5–2.0 times increase compared with baseline) or increase of ≥0.3 mg/dl (≥26.4 µmol/L) • Stage 2: … to 200–299% (2.0–3.0 times increase compared with baseline) • Stage 3: … serum creatinine of ≥4.0 mg/dL	ACUTE KIDNEY INJURY (AKI) (AKIN System) — • Stage 1: … to 150–199% (1.5–1.99 × increase compared with baseline) OR increase of ≥0.3 mg/dl (≥26.4 mmol/L) • Stage 2: … to 200–299% (2.0–2.99 × increase compared with baseline) • Stage 3: … serum creatinine of ≥4.0 mg/dL	Updated per VARC-2 manuscript

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

Section Modified	Text as Written in REPRISE II Protocol Version AA		Text as Written in REPRISE II Protocol Version AB		Justification for Modification
		(≥354 µmol/L) with an acute increase of at least 0.5 mg/dL (44 µmol/L) … urine output (up to 7 days): • Stage 1: … more than 6 hours • Stage 2: … more than 12 hours • Stage 3: Less than 0.5 ml/kg per hour for more than 24 hours or anuria		(≥354 mmol/L) with an acute increase of at least 0.5 mg/dL (44 mmol/L) … urine output (up to 7 days): • Stage 1: …>6 but <12 hours • Stage 2: … >12 but <24 hours • Stage 3: <0.3 ml/kg per hour for ≥24 hours or anuria for ≥12 hours	
	ARRHYTHMIA	… major arrhythmias. … The therapeutic approach to new-onset AF should be documented (spontaneous, electrical or medical cardioversion, limitation of oral anticoagulation and rate or rhythm control).	ARRHYTHMIA	… 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]). …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	Life-threatening or Disabling Bleeding • Fatal bleeding -OR- • … compartment syndrome -OR- • … surgery -OR- • Overt… units Major Bleeding • Overt … blood/RBC -AND- Minor Bleeding	BLEEDING	Life-threatening or Disabling Bleeding • Fatal bleeding (Bleeding Academic Research Consortium [BARC] type 5) • … compartment syndrome (BARC type 3b and 3c) • … surgery (BARC type 3b) • Overt… units (BARC type 3b) Major Bleeding (BARC type 3a) • Overt … blood/RBC, or causing hospitalization or permanent injury, or requiring surgery … Minor Bleeding (BARC type 2 or 3a, depending on the severity)	

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

Section Modified	Text as Written in REPRISE II Protocol Version AA	Text as Written in REPRISE II Protocol Version AB	Justification for Modification
		CONDUCTION DISTURBANCES: Implant-related new or worsened cardiac conduction disturbances include new or worsened first degree atrioventricular (AV) block, second degree AV block (Mobitz I or Mobitz II), third degree AV block, incomplete right bundle branch block (RBBB), RBBB, intraventricular conduction delay, left bundle branch block (LBBB), left anterior fascicular block, or left posterior fascicular block, including block requiring permanent pacemaker implant Note 1: High grade AV block is considered persistent if it is present every time the underlying rhythm is checked. Note 2: See also definitions for arrhythmia and permanent pacemaker.	
		CONVERSION TO OPEN SURGERY: Conversion to open sternotomy during the TAVR procedure secondary to any procedure-related complications	
	DEATH: Cardiovascular Death • … or other vascular disease Procedure-Related Death Death related to valve implantation that occurs within 48 hours of index procedure	DEATH: Cardiovascular Death • … 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 Non-cardiovascular Death Any death in which the primary cause of death is clearly related to another condition (e.g. trauma, cancer, suicide)	

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

Section Modified	Text as Written in REPRISE II Protocol Version AA	Text as Written in REPRISE II Protocol Version AB	Justification for Modification
	DEVICE MIGRATION: …from its original implant location confirmed by X-ray, echocardiography, CT scan or MRI or valve migration demonstrated by direct assessment during open heart surgery or at autopsy.	DEVICE MIGRATION: … 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 …	
		FRAILTY: Slowness, weakness, exhaustion, wasting and malnutrition, poor endurance and inactivity, loss of independence.	
		HOSTILE CHEST: Any of the following or other reasons that make redo operation through sternotomy or right anterior thoracotomy prohibitively hazardous: • Abnormal chest wall anatomy due to severe kyphoscoliosis or other skeletal abnormalities (including thoracoplasty, Potts' disease • Complications from prior surgery • Evidence of severe radiation damage (e.g. skin burns, bone destruction, muscle loss, lung fibrosis or esophageal stricture) • History of multiple recurrent pleural effusions causing internal adhesions	
		INTERNAL MAMMARY ARTERY…: 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	

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

Section Modified	Text as Written in REPRISE II Protocol Version AA		Text as Written in REPRISE II Protocol Version AB		Justification for Modification
				posterior table.	
			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	
	MYOCARDIAL INFARCTION (MI)	**Periprocedural MI (≤72 hours after the index procedure)** • … hemodynamic instability, or imaging… -AND- • Elevated … consisting of 2 or more post-procedure samples that are >0.6 to 8 h apart with a 20% increase in the second sample and a peak value exceeding 15× the 99th percentile URL (troponin), or a peak value exceeding 5× the 99th percentile URL (CK-MB) with new pathological Q waves in at least 2 contiguous leads **Spontaneous MI (>72 hours after the index procedure)** • … cardiac biomarkers with at least … following o ECG changes …	MYOCARDIAL INFARCTION (MI)	**Periprocedural MI (≤72 hours after the index procedure)** • … hemodynamic instability, new pathological Q waves in at least two contiguous leads, or imaging … -AND- • Elevated … 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)** • … cardiac biomarkers (preferably troponin) with at least … following o Symptoms of ischemia o ECG …	
	PARAVALVULAR LEAK (as measured by	Leakage due… Diagnosis of paravalvular leak may be obtained from TEE, however…	PARAVALVULAR REGURGITATION	Leakage due … Diagnosis of paravalvular regurgitation may be obtained from TEE/TTE; however…	Revised for clarity

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

Section Modified	Text as Written in REPRISE II Protocol Version AA	Text as Written in REPRISE II Protocol Version AB	Justification for Modification
	TEE)		
	PERMANENT PACEMAKER (PPM) IMPLANTATION: Implantation … new conduction disturbances… • Procedure-related: … new onset conduction disturbances…	PERMANENT PACEMAKER (PPM) IMPLANTATION: Implantation … new or worsened conduction disturbances … • Procedure-related: … new onset or worsened conduction disturbances… Note: See also definitions for arrhythmia and conductance disturbance.	Updated per VARC-2 manuscript. Added per VARC-2 manuscript.
		PORCELAIN AORTA: Heavy circumferential calcification of the entire ascending aorta extending to the arch such that aortic cross-clamping is not feasible	
	RIGHT VENTRICULAR INSUFFICIENCY: • Defined as … o Edema	RIGHT VENTRICULAR INSUFFICIENCY: • Defined as … 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.	
	STROKE: Stroke is an acute symptomatic episode of neurological dysfunction attributed to a vascular cause. **Subclassifications of stroke** • Ischemic Stroke is defined as an acute symptomatic episode ... • Hemorrhagic Stroke … acute symptomatic episode of focal … caused by a nontraumatic intraparenchymal… Note 1: The CEC will adjudicate ischemic versus hemorrhagic stroke. **Stroke diagnostic criteria…** • Duration of a focal or global neurological deficit ≥24 h; **OR** <24 h, if therapeutic intervention(s) were performed (e.g. thrombolytic therapy or intracranial angioplasty); **OR** available neuroimaging	STROKE[44,48]: 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.... • Hemorrhagic Stroke … acute episode of focal … caused by an intraparenchymal… Note 1: The CEC will adjudicate ischemic versus hemorrhagic stroke. Note 2: A stroke may be classified as undetermined if there is insufficient information to allow categorization as ischemic or hemorrhagic **Stroke diagnostic criteria…** • Duration of a focal or global neurological	

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

Section Modified	Text as Written in REPRISE II Protocol Version AA	Text as Written in REPRISE II Protocol Version AB	Justification for Modification
	documents a new hemorrhage or infarct; **OR** the neurological deficit results in death • No other … influences) • Confirmation … o Neuroimaging procedure (MRI or CT scan or cerebral angiography) o Lumbar puncture (i.e., spinal fluid analysis diagnostic of intracranial hemorrhage) Note 2: Subjects … neuroimaging studies. **Stroke definitions** Diagnosis as above, preferably with positive neuroimaging study • Non-disabling: Modified Rankin score (MRS) <2 at 90 days OR an increase in MRS of ≤1. • Disabling: Modified Rankin score ≥2 at 90 days AND an increase in MRS of ≥1. Note 3: Modified Rankin score assessments should be made by qualified individuals according to a certification process. If there is discordance between the 30 and 90 day Modified Rankin scores, a final determination of major versus minor stroke will be adjudicated by the CEC.	deficit ≥24 h; OR <24 h, if available neuroimaging documents a new hemorrhage or infarct; OR the neurological deficit results in death • No other … influences), to be determined by or in conjunction with designated neurologist • Confirmation … o Neuroimaging procedure (MRI or CT scan), but stroke may be diagnosed on clinical grounds alone Note 3: Subjects … neuroimaging studies (CT scan or brain MRI). **Stroke definitions** Diagnosis as above, preferably with positive neuroimaging study • Non-disabling: Modified Rankin Scale (mRS) score <2 at 90 days OR one that does not result in an increase of at least one mRS category from an individual's pre-stroke baseline • Disabling: Modified Rankin Scale score ≥2 at 90 days AND an increase of at least one mRS category from an individual's pre-stroke baseline Note 4: Modified Rankin Scale assessments should be made by qualified individuals according to a certification process. Note 5: Assessment of the mRS score should occur at all scheduled visits in a study; mRS also should be performed after a stroke and at 90 days after the onset of any stroke.	
	STRUCTURAL VALVE DETERIOR: • Valve-related dysfunction: indexed effective orifice area <0.85 cm2/m2 [≤0.7 cm^2/m^2 for BMI≥30 kg/m^2] and mean aortic valve gradient ≥20 mmHg or peak	STRUCTURAL VALVE DETERIOR: Component of time-related valve safety defined as follows: • Valve-related dysfunction: Mean aortic valve gradient ≥20 mmHg, EOA	

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

Section Modified	Text as Written in REPRISE II Protocol Version AA	Text as Written in REPRISE II Protocol Version AB	Justification for Modification
	ATION: velocity ≥3 m/s, or moderate or severe prosthetic valve regurgitation)	ATION: ≤0.9-1.1 cm^2, and/or DVI <0.35 AND/OR moderate or severe prosthetic valve regurgitation (per VARC definition)	
	TAV-IN-TAV DEPLOYMENT: An additional valve prosthesis is implanted within a previously implanted prosthesis because of suboptimal device position and function during or after the index procedure.	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): • New focal neurological deficit with rapid symptom resolution (usually 1 to 2 h), always within 24 hours • Neuroimaging without tissue injury (if performed)	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.	
		UNPLANNED USE OF CPB: Unplanned use of cardiopulmonary bypass (CPB) for hemodynamic support at any time during the TAVR procedure	
	VALVE MIGRATION: After initial correct positioning the valve prosthesis moves upward or downward within the aortic annulus from its initial position, with or without regurgitation.	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: Prosthetic heart valve dysfunction includes indexed effective orifice area <0.85 cm^2/m^2 [≤0.7 cm^2/m^2 for BMI≥30 kg/m^2] and either a mean aortic valve gradient ≥20 mm Hg or a peak velocity ≥3m/sec, OR moderate or severe prosthetic valve aortic 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: The need for hospitalization associated with valve-related symptoms or worsening CHF	

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

Section Modified	Text as Written in REPRISE II Protocol Version AA		Text as Written in REPRISE II Protocol Version AB		Justification for Modification
			SYMPTOMS/CHF REQUIRING HOSPITALIZATION	(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.	
	VASCULAR ACCESS SITE AND ACCESS RELATED COMPLICATIONS	**Major Vascular Complications** • Any thoracic aortic dissection • Access site … compartment syndrome) leading to either death, need for significant blood transfusions (≥4 units), unplanned percutaneous or surgical intervention, or irreversible end-organ damage (e.g., hypogastric artery occlusion causing visceral ischemia or spinal artery injury causing neurologic impairment) • Distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage **Minor Vascular Complications** • Access site or access-related vascular injury (dissection, stenosis, perforation,	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 … 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	

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

Section Modified	Text as Written in REPRISE II Protocol Version AA	Text as Written in REPRISE II Protocol Version AB	Justification for Modification
	rupture, arterio-venous fistula, or pseudoaneurysm requiring compression or thrombin injection therapy, or hematoma requiring transfusion of ≥2 but <4 units) not requiring unplanned percutaneous or surgical intervention and not resulting in irreversible end-organ damage Distal embolization treated with embolectomy and/or thrombectomy and not resulting in amputation or irreversible end-organ damage **Closure Device Failure** Failure of percutaneous access site closure resulting in interventional (e.g., stent-graft) or surgical correction and not associated with death, need for significant blood transfusions (≥4 units), or irreversible end-organ damage. Pre-planned surgical access or prophylactic endovascular approach …	• Any new ipsilateral lower extremity ischemia documented by patient symptoms, physical exam, and/or decreased or absent blood flow on lower extremity angiogram • Surgery for access site-related nerve injury • Permanent access site-related nerve injury **Minor Vascular Complications** • Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysms , hematomas, percutaneous closure device failure*) not leading to death, life-threatening or major bleeding**, visceral ischaemia or neurological impairment • Distal embolization treated with embolectomy and/or thrombectomy and not resulting in amputation or irreversible end-organ damage • Any unplanned endovascular stenting or unplanned surgical intervention not meeting the criteria for a major vascular complication • Vascular repair or the need for vascular repair (via surgery, ultrasound-guided compression, transcatheter embolization, or stent-graft) ***Percutaneous Closure Device Failure** Failure of a closure device to achieve hemostasis at the arteriotomy site leading to alternative treatment (other than manual compression or adjunctive endovascular ballooning) Note 1**:** Pre-planned surgical access or a	

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

Section Modified	Text as Written in REPRISE II Protocol Version AA	Text as Written in REPRISE II Protocol Version AB	Justification for Modification
		planned endovascular approach to vascular closure (e.g., "pre-closure")[52,5368,69] should be considered as part of the TAVR procedure and not as a complication, unless untoward clinical consequences are documented (e.g., bleeding complications, limb ischemia, distal embolization, or neurological impairment). Note 2: If unplanned percutaneous or surgical intervention does not lead to adverse outcomes this is not considered a major vascular complication. ** Refers to VARC bleeding definitions	
		VENTRICULAR SEPTAL PERFORATION: Angiographic or echocardiographic evidence of a new septal perforation during or after the TAVR procedure	
27. Appendices		27.1-1 Changes-Protocol Version AA to Version AB Table 27.1-1 lists changes between protocol versions AA and AB Added Table 27.1-1.	Added to show document version changes.

Table 27.1-2: Table of Changes for REPRISE II Protocol Version AC (Compared to REPRISE II Protocol Version AB)

Section Modified	Text as Written in REPRISE II Protocol Version AB	Text as Written in REPRISE II Protocol Version AC	Justification for Modification
2. Protocol Synopsis Exclusion…	EC 17 … treating physician and/or heart team, is clinically...	EC 17 … treating physician, is clinically...	Updated for clarity
11. Study Methods	Figure 11.1-1 REPRISE Study Design	Figure 11.1-1 REPRISE Study Design Updated symbol for procedural cine-angiography at index procedure.	

Table 27.1-2: Table of Changes for REPRISE II Protocol Version AC (Compared to REPRISE II Protocol Version AB)			
Section Modified	**Text as Written in REPRISE II Protocol Version AB**	**Text as Written in REPRISE II Protocol Version AC**	**Justification for Modification**
11. Study Methods Table 11.1-1	o: Annual imaging… must be performed. If additional...	o: Annual imaging… must be performed. Results must be forwarded to the CT/X-Ray Core Laboratory for analysis. If additional…	
	r: Final post-deployment aortogram of the ascending aorta should be performed and sent to the CT Core Laboratory.	r: Procedural cine-angiogram including final post-deployment aortogram of the ascending aorta should be sent to the CT/X-Ray Core Laboratory for analysis.	
11.7.3 Preparing and Using …	9) A final post-deployment aortogram … forwarded to the Core Laboratory for analysis.	9) A final post-deployment aortogram … forwarded with the procedural cine-angiogram to the Core Laboratory for analysis.	
27. Appendices		27.1-2 Changes-Protocol Version AB to Version AC Table 27.1-2 lists changes between protocol versions AB and AC Added Table 27.1-2.	Added to show document version changes.

Table 27.1-3: Table of Changes for REPRISE II Protocol Version AD (Compared to REPRISE II Protocol Version AC)			
Section Modified	**Text as Written in REPRISE II Protocol Version AC**	**Text as Written in REPRISE II Protocol Version AD**	**Justification for Modification**
2. Protocol Synopsis, Exclusion Criteria and Section 9.3 Exclusion Criteria	EC1. Subject has a unicuspid or bicuspid aortic valve.	EC1. Subject has a congenital unicuspid or bicuspid aortic valve.	Updated for clarity.
2. Protocol Synopsis Adjunctive Pharmacologic Therapy and Section 11.6 Preprocedure Medications	Note 2: If a subject requires chronic anticoagulation (e.g., warfarin, dabigatran, etc.), either clopidogreld or aspirin is required in addition to the anticoagulant therapy post-procedure (but both aspirin and clopidogrel are not required).	Note 2: If a subject requires chronic anticoagulation (e.g., warfarin, dabigatran, etc.), either clopidogreld or aspirin is required prior to and after implant procedure in addition to the anticoagulant therapy post-procedure (but both aspirin and clopidogrel are not required). Note 3: If a subject requires chronic anticoagulation (e.g., warfarin, dabigatran, etc.), either clopidogrel or aspirin is required prior to implant procedure (but both aspirin and	Updated for clarity and to account for local practice.

Table 27.1-3: Table of Changes for REPRISE II Protocol Version AD (Compared to REPRISE II Protocol Version AC)			
Section Modified	**Text as Written in REPRISE II Protocol Version AC**	**Text as Written in REPRISE II Protocol Version AD**	**Justification for Modification**
		clopidogrel are not required).	
11. Study Methods Table 11.1-1 and Section 11.4 Screening Assessments	l: A coronary angiogram must be performed within 180 days prior to the index procedure and should be performed within 90 days, if possible, to assess extent of aortic stenosis and coronary artery status. o A coronary angiogram must be performed within 180 days prior to the index procedure and should be performed within 90 days, if possible; simultaneous aortogram and hemodynamics indicating ascending aorta/left ventricle (AO/LV) pressure measurements should be performed to assess the extent of aortic stenosis and coronary artery status.	l: A coronary angiogram must be performed within 365 days prior to the index procedure. If there is concern regarding the current extent of coronary artery disease or aortic stenosis, the Case Review Committee may recommend a repeat study closer to the time of enrollment. o A coronary angiogram must be performed within 365 days prior to the index procedure. If there is concern regarding the current extent of coronary artery disease or aortic stenosis, the Case Review Committee 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 during the cardiac catheterization.	Expanded window allowed for coronary angiogram so as to minimize the need for unnecessary repetition of invasive tests in an elderly patient population while still ensuring that adequate assessment of coronary artery disease and aortic stenosis is performed. Note that similar change is made in Section 11.4 Screening Assessments (Imaging assessments).

Table 27.1-4: Table of Changes for REPRISE II Protocol Version AE (Compared to REPRISE II Protocol Version AD)			
Section Modified	**Text as Written in REPRISE II Protocol Version AD**	**Text as Written in REPRISE II Protocol Version AE**	**Justification for Modification**
2. Protocol Synopsis, Sample Size Parameters	• Test significance level (α) = 0.05 (1-sided) • Power ≥ 90%	• Test significance level (α) = 0.025 (1-sided) • Power ≥ 80%	Updated per regulatory agency request.

Table 27.1-4: Table of Changes for REPRISE II Protocol Version AE (Compared to REPRISE II Protocol Version AD)

Section Modified	Text as Written in REPRISE II Protocol Version AD	Text as Written in REPRISE II Protocol Version AE	Justification for Modification
2. Protocol Synopsis, Success Criteria	The Pocock alpha spending function is used to adjust the alpha-level for each analysis: 0.02246, 0.01704, and 0.02799, respectively.	The Pocock alpha spending function is used to adjust the alpha-level for each analysis: 0.01123, 0.00792, and 0.01305, respectively.	
12.1.1.1 Primary Device Performance Endpoint	The alpha-level for the interim and final analyses is adjusted using the Pocock alpha spending function method for unequal information time intervals[62]; they are 0.02246, 0.01704, and 0.02799, respectively.	The alpha-level for the interim and final analyses is adjusted using the Pocock alpha spending function method for unequal information time intervals[62]; they are 0.01123, 0.00792, and 0.01305, respectively.	
12.1.1.2 Sample Size - Primary Device Performance Endpoint	• Test significance level (α) = 0.05 (1-sided) • Power ≥ 90%	• Test significance level (α) = 0.025 (1-sided) • Power ≥ 80%	
12.3.2 Interim Analyses	… on the full enrolled cohort. The Pocock alpha spending function method for unequal information time intervals[62] is used to adjust the alpha-level for each analysis: 0.02246, 0.01704, and 0.02799, respectively.	… on the full enrolled cohort. The Pocock alpha spending function method for unequal information time intervals[62] is used to adjust the alpha-level for each analysis: 0.01123, 0.00792, and 0.01305, respectively.	

Table 27.1-5: Table of Changes for REPRISE II Protocol Version AF (Compared to REPRISE II Protocol Version AE)

Section Modified	Text as Written in REPRISE II Protocol Version AE	Text as Written in REPRISE II Protocol Version AF	Justification for Modification
Sponsor	Sadra Medical, Inc., A Subsidiary of Boston Scientific Corporation	Boston Scientific Structural Heart a Division of Boston Scientific Corporation	Sponsor name updated
Clinical Contacts		Anne Cornaille Senior Clinical Trial Manager– Interventional Cardiology Boston Scientific Parc Val Saint Quentin 2 Rue René Caudron, Bâtiment H 78960 Voisins-le-Bretonneux, France	Additional clinical trial manager
Footer (all)		Added: S2266/S2290	Clarification for cross referencing other study-related documents

Table 27.1-5: Table of Changes for REPRISE II Protocol Version AF (Compared to REPRISE II Protocol Version AE)

Section Modified	Text as Written in REPRISE II Protocol Version AE	Text as Written in REPRISE II Protocol Version AF	Justification for Modification
2. Protocol Synopsis Device Sizes	…annulus diameter between ≥19 mm and…	…annulus diameter between ≥20 mm and…	Change made in response to current study observations
2. Protocol Synopsis Control Device	Control Device For the device performance primary endpoint, a performance goal (PG) based on the 30-day mean aortic valve pressure gradient derived from published literature will be used as the control for analysis.	Comparator For the device performance primary endpoint, a performance goal (PG) based on the 30-day mean aortic valve pressure gradient derived from published literature will be used as the comparator for analysis. For the primary safety endpoint, a performance goal (PG) based on 30 day all-cause mortality data derived from published literature will be used as the comparator for analysis.	Clarification that there is a comparator, not a control device. Also, a primary safety endpoint will be assessed on the combined main trial and extended trial cohorts.
2. Protocol Synopsis Study Design	… high risk for surgical aortic valve replacement (SAVR). A total of up to 120 subjects will be enrolled in the study at up to 15 centers. Two planned interim analyses based on the primary endpoint at 30 days post-implant procedure will be performed on the first 40 and 60 enrolled subjects. The REPRISE II study will be conducted in accordance with the relevant parts of the International … Helsinki; the International Conference on Harmonisation…	… high risk for surgical aortic valve replacement (SAVR). A total of up to 120 subjects will be enrolled in the main study at up to 15 centers. Subsequently, up to 130 additional subjects will be enrolled at up to 21 centers in the extended trial cohort. The statistical hypotheses for the main trial cohort and the combined (main + extended) cohorts are described below. The REPRISE II study will be conducted in accordance with the International … Helsinki; the relevant parts of the International Conference on Harmonisation…	Clarification
2. Protocol Synopsis Planned Number of Subjects	A total enrollment of up to 120 subjects is planned.	A total enrollment of up to 120 subjects is planned for the main study. Subsequently, up to 130 additional subjects (250 subjects in total) will be enrolled in the extended trial cohort.	
2. Protocol Synopsis Planned Number of	Up to 15 centers in these possible countries: Australia, France, Germany and United Kingdom.	The main study will enroll subjects at up to 15 centers in these possible countries: Australia, France, Germany and United Kingdom. The extended trial cohort will enroll subjects at up to 21	

Table 27.1-5: Table of Changes for REPRISE II Protocol Version AF (Compared to REPRISE II Protocol Version AE)			
Section Modified	**Text as Written in REPRISE II Protocol Version AE**	**Text as Written in REPRISE II Protocol Version AF**	**Justification for Modification**
Centers…		centers in Australia and European countries.	
2. Protocol Synopsis Secondary Endpoints	• Device Success based on the Valve Academic Research Consortium (VARC)[a] o Absence of procedural mortality o Correct positioning of a single transcatheter valve into the proper anatomical location oIntended performance of the Lotus Valve (indexed effective orifice area >0.85 cm^2/m^2 [>0.7 cm^2/m^2 for BMI ≥30 kg/ m^2] plus either a mean aortic valve gradient <20 mm Hg or a peak velocity <3m/sec, without moderate or severe prosthetic valve aortic regurgitation) **Note:** At least… a: Serruys P, *et al.* (2012) VARC Clinical Research Updates: Important Changes from VARC-2. Transcatheter Valve Therapeutics, Seattle, US (manuscript pending publication).	• Device Success based on the Valve Academic Research Consortium definitions (VARC)[a, b] **Note:** At least… a: Kappetein AP, et al. J Am Coll Cardiol. 2012;60:1438 b: Leon MB, et al. J Am Coll Cardiol. 2011;57:253	Indicate both VARC 1 and VARC 2 definitions here to be able to pool REPRISE II outcomes with data from REPRISE I (which used VARC 1 definitions) and to compare with published data using VARC 1 definitions.
2. Protocol Synopsis Additional Measurements	***Note 4:*** For subjects diagnosed with a neurological event (e.g., stroke, transient ischemic attack), a neurological physical exam, NIHSS assessment, and mRS must be performed after the event; mRS must also be administered at 90 days post-neurological event.	***Note 4:*** A total enrollment of up to 120 subjects is planned for the main study. Subsequently, up to 130 additional subjects will be enrolled for the extended trial cohort. In the main study, for subjects diagnosed with a neurological event (e.g., stroke, transient ischemic attack), a neurological physical exam, NIHSS assessment, and mRS must be performed after the event; mRS must also be administered at 90 days post-neurological event. In the extended trial cohort, for subjects diagnosed with a neurological event, NIHSS assessment and mRS must be performed after the event; mRS must also be administered at 90 days post-neurological event; the neurological physical exam is not required in the extended trial cohort.	
2. Protocol Synopsis Inclusion Criteria	IC3. ..aortic annulus size between ≥19 and…	IC3. …annulus size between ≥20 mm and…	Change made in response to current study observations

Table 27.1-5: Table of Changes for REPRISE II Protocol Version AF (Compared to REPRISE II Protocol Version AE)

Section Modified	Text as Written in REPRISE II Protocol Version AE	Text as Written in REPRISE II Protocol Version AF	Justification for Modification
2. Protocol Synopsis Exclusion Criteria	EC16. Subject has any therapeutic invasive cardiac procedure within… EC24. Subject has preexisting untreated conduction system disorder (e.g., Type II second degree atrioventricular block) that requires new pacemaker implantation.	EC16. Subject has any therapeutic invasive cardiac procedure (including balloon aortic valvuloplasty) within… 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.	Clarification
2. Protocol Synopsis Statistical Methods	Statistical Methods	Statistical Methods – Main Trial Cohort (N=120)	Updated statistical methods including addition of a statistically powered safety endpoint
2. Protocol Synopsis Sample Size Parameters	• Two planned … performed on the first … • A final analysis will be performed on all subjects (120) • … Note 2: The alpha-level for the interim and final analyses is adjusted using the Pocock alpha spending function (see Success Criteria below).	• Two planned … performed on the first … • A final analysis will be performed on all subjects enrolled in the main trial cohort (120 subjects) • … Note 2: The alpha-level for the interim and final analyses of the main trial cohort is adjusted using the Pocock alpha spending function (see Success Criteria below).	
2. Protocol Synopsis Success Criteria	Two interim analyses will be conducted on the first 40 and 60 subjects and a final analysis will be conducted on the fully enrolled cohort. The Pocock…	Two interim analyses will be conducted on the first 40 and 60 subjects and a final analysis will be conducted on the fully enrolled main trial cohort (N=120). The Pocock…	
2. Protocol Synopsis Statistical Methods		Statistical Methods – Combined Main and Extended Trial Cohort (N=250)	
2. Protocol Synopsis Primary Statistical Hypothesis		All-cause mortality at 30 days post implant procedure is less than the PG of 16 % (expected rate of 9.8% + testing margin of 6.2%)	

Table 27.1-5: Table of Changes for REPRISE II Protocol Version AF (Compared to REPRISE II Protocol Version AE)			
Section Modified	**Text as Written in REPRISE II Protocol Version AE**	**Text as Written in REPRISE II Protocol Version AF**	**Justification for Modification**
2. Protocol Synopsis Statistical Test Methods		A one-sample z-test will be used to test the one-sided hypothesis: H0: $Mortality_{30D} \geq PG$ H1: $Mortality_{30D} < PG$ where $Mortality_{30D}$ is the 30-day all-cause mortality rate for the Lotus Valve and PG is 16%.	
2. Protocol Synopsis Sample Size Parameters		• Expected 30-day all-cause mortality rate = 9.8% • Performance goal (PG) = 16 % (expected rate of 9.8% + testing margin of 6.2%) • Test significance level (α) = 0.025 (1-sided) • Power ($1 - \beta$) = 80% • Expected rate of attrition = 2% • Planned enrollment of up to 250 subjects (main trial cohort enrollment of 120 subjects plus extended trial cohort enrollment of 130 subjects) ***Note***: The expected 30-day all-cause mortality rate is assumed to be 9.8% based on a literature review of studies evaluating the Medtronic CoreValve System and the Edwards Lifesciences SAPIEN Transcatheter Heart Valve System.	
2. Protocol Synopsis Success Criteria		If the *P* value from the one-sample z-test is <0.025, it will be concluded that the primary safety endpoint for the Lotus Valve is less than the PG. This corresponds to the one-sided upper 97.5% confidence bound of the observed 30 day mortality rate being <16 %.	
4 Introduction	This protocol specifies … manufactured by Sadra Medical, a Subsidiary… (BSC). The Lotus Valve System… If needed, the valve... prior to final release. The valve… **4.1. Justification for the Use of the Investigational Device in Human Subjects**	This protocol specifies… manufactured by Boston Scientific Structural Heart a Division of Boston Scientific Corporation. The Lotus Valve System... If needed, the valve... prior to final release or can be fully retrieved if during the procedure the decision is made not to implant. The valve…	Clarification of sponsor name and valve information. Updated information on TAVR (additional

Table 27.1-5: Table of Changes for REPRISE II Protocol Version AF (Compared to REPRISE II Protocol Version AE)

Section Modified	Text as Written in REPRISE II Protocol Version AE	Text as Written in REPRISE II Protocol Version AF	Justification for Modification
	The incidence…, has rapidly accumulated through observational studies[8,9], 10device-specific registries[11-17], national registries[18-20], and randomized controlled trials[21,22]. An expert consensus document on TAVR was recently published[23]. The prospective, single arm,… through 5 years. To date, the study has reached the primary endpoint, which was achieved… and 1 major stroke, which was based on preliminary adjudication by the CEC and is pending full adjudication based on an assessment to be performed at 90-day follow-up. Paravalvular regurgitation… acute safety and performance of the Lotus Valve System. **4.2 Justification for the Study Design** As noted above… These include an enhanced…	**4.1. Justification for the Use of the Investigational Device in Human Subjects** **4.1.1 Treatment for Aortic Stenosis** The incidence…, valve has rapidly accumulated through observational studies[8-15], device-specific registries[16-22], national registries[23-26], and randomized controlled trials[21,22]. Through 2-year follow-up in the PARTNER US IDE trial there have been significant reductions in mortality and repeat hospitalization rates compared to standard medical therapy in subjects unsuitable for SAVR[29], and similar mortality rates compared to surgical valve replacement in high-surgical-risk subjects[30]. An expert consensus document on TAVR was recently published[31]. **4.1.2. REPRISE I Study** The aforementioned results notwithstanding, TAVR with early generation devices has been associated with increased stroke risk versus surgical valve replacement[28,30]. Cerebrovascular accidents and vascular complications associated with TAVR have been significant predictors of mortality[38,39]. The paravalvular regurgitation more commonly seen with TAVR compared to surgery has also been accompanied by higher early and late mortality[21,30,40]. While careful subject selection may serve to mitigate these risks[41-43], device design improvements such as seen with the Lotus Valve System (Section 5.1) may enable more precise placement, minimize or eliminate paravalvular regurgitation, and obviate the need for valve-in-valve repeat intervention. The prospective, single arm,… through 5 years. The primary endpoint was achieved… and 1 major stroke. To date, data are available through 3 months[47]. There were no additional MACCE events beyond the primary endpoint. The 3-month VARC[44] combined safety endpoint, including	published literature) and updated REPRISE I study results to include 3-month data.

Table 27.1-5: Table of Changes for REPRISE II Protocol Version AF (Compared to REPRISE II Protocol Version AE)			
Section Modified	**Text as Written in REPRISE II Protocol Version AE**	**Text as Written in REPRISE II Protocol Version AF**	**Justification for Modification**
		MACCE, life threatening/disabling bleeding, major vascular complications, and Stage 3 acute kidney injury, was 3/11 (1 small left femoral dissection treated with balloon inflation during the procedure; 2 life-threatening/disabling bleeds through 30 days that were unrelated to valve implantation and resolved). Conduction disturbances led to implantation of a permanent pacemaker before discharge in 4 subjects; 2 of these 4 subjects were pacemaker dependent at 3 months. While all REPRISE I subjects were NYHA Class II (n=6) or III (n=5) at baseline, this distribution was significantly improved by 3 months (7 in Class I, 3 in Class II, 1 in Class III; *P*=0.004). The mean aortic valve gradient was 12.0±2.2 mmHg for the cohort and was below the VARC criterion of 20 mmHg in all subjects at 3 months, with no moderate or severe paravalvular aortic regurgitation. … acute safety and performance of the Lotus Valve System. **Table 4.1-1** has been updated with 7 additional references. **4.2 Justification for the Study Design** As noted above... These include a pre-loaded delivery system, early leaflet function to maintain hemodynamic stability during valve deployment, an enhanced…	
5.3 Device Labeling	• Part/Reference number • Lot number • Expiration (use by)… The following statement appears on the label. CAUTION: Exclusively for Clinical Investigations.	• Part/Reference number • Lot number (matches the lot number on the handle) • Valve size • Expiration (use by)… • Temperature storage requirements The following statement appears on the label. CAUTION: Exclusively for Clinical Investigations. Device labeling will be provided in local language(s) as per respective national regulations.	Clarification
7.1 Primary Endpoints	The primary device…	The primary device… The primary analysis population will be the subject population implanted with the Lotus Valve. Outcomes in this as-treated subject population in the main	Clarification of the cohorts assessed for each primary

Table 27.1-5: Table of Changes for REPRISE II Protocol Version AF (Compared to REPRISE II Protocol Version AE)

Section Modified	Text as Written in REPRISE II Protocol Version AE	Text as Written in REPRISE II Protocol Version AF	Justification for Modification
	The primary safety…	trial cohort (N=120) will be compared to a performance goal (PG; see Section 12.1.1.1). The primary safety… The primary safety endpoint will be evaluated on an intention-to-treat (ITT) basis (all subjects enrolled, whether or not a study device is implanted). Outcomes in the combined main and extended trial cohort (N=250) will be compared to a PG (see Section 12.1.1.3).	endpoint.
7.2 Secondary Endpoints	Secondary endpoints are listed below. • Device Success post implant procedure[48] o Absence of procedural mortality o Correct positioning of a single transcatheter valve into the proper anatomical location o Intended performance of the Lotus Valve (indexed effective orifice area >0.85 cm^2/m^2 [>0.7 cm^2/m^2 for BMI ≥30 kg/m^2] plus either a mean aortic valve gradient <20 mm Hg or a peak velocity <3m/sec, without moderate or severe prosthetic valve aortic regurgitation) **Note:** At least…	Secondary endpoints are listed below and will be evaluated on an ITT basis. Definitions can be found in Table 26.2 1. • Device Success based on the Valve Academic Research Consortium (VARC)[44, 48] **Note:** At least…	Clarification To be able to pool REPRISE II outcomes with data from REPRISE I (which used VARC 1 definitions) and to compare with published data using VARC 1 definitions.
7.3 Additional Measurements	***Note 4:*** For subjects diagnosed … post-neurological event.	***Note 4***: In the main trial cohort (N=120), for subjects diagnosed … post-neurological event (see Table 11.1-1). In Among the 130 subjects subsequently enrolled (extended trial cohort), for subjects diagnosed with a neurological event, NIHSS assessment and mRS must be performed after the event; mRS must also be administered at 90 days post neurological event; the neurological physical exam is not required (see Table 11.1-2).	Clarify that a neurological physical examination is not required for the extended trial cohort.
8.3 Study Design Justification	In order to support … to risk, a total of up to 120 subjects will be enrolled in the study at up to 15 centers. Safety and device performance results will be reported on all subjects. Planned… subjects.	In order to support …to risk, a total of up to 120 subjects will be enrolled in the main trial cohort at up to 15 centers in these possible countries: Australia, France, Germany and United Kingdom. Planned … subjects and a final analysis will be conducted on the main trial cohort (N=120). Subsequently, up to 130 additional subjects will be enrolled at up to 21 centers	Explain that the main trial cohort consists of 120 subjects and the extended trial cohort will have 130

Table 27.1-5: Table of Changes for REPRISE II Protocol Version AF (Compared to REPRISE II Protocol Version AE)

Section Modified	Text as Written in REPRISE II Protocol Version AE	Text as Written in REPRISE II Protocol Version AF	Justification for Modification
		in Australia and European countries and a statistically powered analysis based on the primary safety endpoint will be performed on the combined main and extended trial cohort (250 subjects).	additional subjects.
9.1 Study Population and Eligibility	The study… and none of the exclusion criteria (Section 9.3).	The study… and none of the exclusion criteria (Section 9.3). All subjects will then be reviewed by the CRC to confirm eligibility and suitability for enrollment in the study.	Clarification
9.2 Inclusion Criteria	Table 9.2-1: Inclusion Criteria IC3. ..aortic annulus size between ≥19 and…	Table 9.2-1: Inclusion Criteria IC3. ..aortic annulus size between ≥20 and…	Change made in response to current study observations
9.3.1 Exclusion Criteria	EC16. Subject has any therapeutic invasive cardiac procedure within… EC 24.Subject has preexisting untreated conduction system disorder (e.g., Type II second degree atrioventricular block) that requires new pacemaker implantation.	EC16. Subject has any therapeutic invasive cardiac procedure (including balloon aortic valvuloplasty) within… EC 24. 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.	Clarification
11. Study Methods	**11.1 Data Collection** The study event schedule is shown diagrammatically in Figure 11.1 1and discussed in Table 11.1 1 and Sections 11.2 through 11.11. Figure 11.1-1 REPRISE Study Design Table 11.1-1: Study Event Schedule AE assessments[s] Device deficiencies, SAE, SADE, USADE, ADE and CEC event assessment e: Neurological…assessors should be independent of the study. For subjects… h: Consists of STS score, logistic euroSCORE and… s: AEs will be… t: Device deficiencies…USADEs, ADEs and CEC…reported to Sadra BSC for…	**11.1 Data Collection** The study event schedules are shown diagrammatically and discussed in Figure 11.1 1and Table 11.1 1 for the main trial cohort (N=120), and in Figure 11.1 2 and Table 11.1 2 for the subsequently enrolled 130 additional subjects (extended trial cohort). Figure 11.1-1 REPRISE Study Design – Main Trial Cohort Table 11.1-1: Study Event Schedule – Main Trial Cohort AE and ADE assessments[s] Device deficiencies, SAE, SADE, USADE, and CEC event assessment e: Neurological…assessors should be independent (not involved with the care of study subjects). For subjects… h: Consists of STS score (2.73), euroSCORE 2011 and… s: AEs and ADEs will be… t: Device deficiencies…USADEs and CEC…reported to	Clarify that the main trial cohort consists of 120 subjects and the extended trial cohort has 130 additional subjects; the assessments removed are not required for subjects enrolled in the extended trial cohort. Note that there are additional changes in Table 111.1-1 and Table 11.1-2 for clarification on STS score, euroSCORE,

Table 27.1-5: Table of Changes for REPRISE II Protocol Version AF (Compared to REPRISE II Protocol Version AE)			
Section Modified	**Text as Written in REPRISE II Protocol Version AE**	**Text as Written in REPRISE II Protocol Version AF**	**Justification for Modification**
		Boston Scientific for… Figure 11.1-2 REPRISE Study Design – Extended Trial Cohort Subject Enrollment Number is 130. Removed symbols for "Neurological Physical Exam" and for "Annual Imaging (Rotational X-ray)" Table 11.1-2: Study Event Schedule – Extended Trial Cohort Removed rows for "Neurological Physical Exam" and for "Annual Imaging (Rotational X-ray)" and updated the footnote numbering accordingly. Added reference to rotational angiogram in footnote as shown below: Procedural cine-angiogram including the final post-deployment aortogram of the ascending aorta (including recommended rotational angiogram of the valve frame) should be sent to the CT/X-Ray Angio Core Laboratory for analysis.	and rotational angiogram of the valve frame. Additional clarifications, including the updating of sponsor name.
11.4 Screening Assessments	Clinical assessments o Risk assessments: STS Score (2.73), euroSCORE 2011, heart team assessment including an in-person evaluation by a cardiac surgeon Imaging assessments o Within 60 days…volume. o A CT angiogram... within 90 days to evaluate… device sizing. It must be performed according to the CT Core Laboratory procedure guidelines…	Clinical assessments o Risk assessments: STS Score (2.73), euroSCORE 2011, heart team assessment including an in-person evaluation by a cardiac surgeon, and any frailty assessments Imaging assessments o Within 60 days…volume. Other echocardiographic measurements include but are not limited to: aortic valve diameter, LVOT, diameter, Sinus of Valsalva diameter, annulus to ventricular apex length, mitral hinge point to apex length. o A CT angiogram... within 90 days, if possible, to evaluate... device sizing. It must meet the CT Core Laboratory procedure guidelines…	Clarification

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Section Modified	Text as Written in REPRISE II Protocol Version AE	Text as Written in REPRISE II Protocol Version AF	Justification for Modification
11.4 Screening Assessments	Figure 11.4-1: Assessment… 19 ---------- 23 ----------27	Figure 11.4-1: Assessment… 20 ---------- 23 ----------27	Change made in response to current study observations
11.5 Baseline Assessments	• Neurological physical examination, which must … assessors should be independent of the study. • NIH Stroke Scale (NIHSS), which must …; assessors…independent of the study • Modified Rankin Scale score, which must …; assessors…independent of the study • The following frailty… assessments will… • 12-lead…must…	• Neurological physical examination required in the main trial cohort, which must ... (see Table 11.1-1); assessors should be independent (not involved with the care of study subjects). A neurological physical examination is not required in the extended trial cohort (see Table 11.1-2). • NIH Stroke Scale (NIHSS), which must …; assessors…independent (not involved with the care of study subjects). • Modified Rankin Scale score, which must …; assessors…independent (not involved with the care of study subjects). • The following frailty… assessments at screening and/or baseline will… • 12-lead… at screening and/or baseline must…	Clarification that a neurological physical examination is not required in the extended trial cohort. Clarification regarding independence of assessors and timing of some assessments
11.7.2	If a significant waist remains after repeated valvuloplasty, it is strongly recommended that the Lotus Valve not be implanted. If the subject is not implanted, then…	If a significant waist remains after repeated valvuloplasty, it is strongly recommended that appropriate valve size be reconsidered or, if annulus size is within the lower measurement of the annulus size, that the Lotus Valve not be implanted. If the subject is not implanted with the Lotus Valve, then…	Clarification
11.7.3 Preparing…	9) A final post-deployment aortogram of the ascending aorta should be performed…	9) A final post-deployment aortogram of the ascending aorta (including recommended rotational angiography of the valve frame) should be performed…	
11.8 Post-Procedure	• Subject's heart rhythm should be monitored using telemetry for at least 48 hours after the index procedure.	• It is recommended that the subject's heart rhythm be monitored using telemetry for at least 48 hours after the index procedure.	
11.9 Prior to Discharge…	• Neurological physical examination, which must be performed by a neurologist or neurology fellow; assessors should be independent of the study.	• Neurological physical examination required in in the main trial cohort, which must be performed by a neurologist or neurology fellow; assessors should be independent (not involved with the care of study subjects;	Clarification regarding independence of assessors.

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	• NIH Stroke Scale (NIHSS), which must …; assessors…independent of the study • Modified Rankin Scale score, which must …; assessors…independent of the study	see Table 11.1-1). A neurological physical examination is not required in the extended trial cohort (see 11.1-2). • NIH Stroke Scale (NIHSS), which must …; assessors…independent (not involved with the care of study subjects). • Modified Rankin Scale score, which must …; assessors…independent (not involved with the care of study subjects).	Clarification that a neurological physical examination is not required in the extended trial cohort. Clarification that rotational X-ray angiography is not required in the extended trial cohort. Clarification that ADE is not reported after 12 months.
11.10.1 11.10.2 11.10.3	• Modified Rankin Scale score, which must …; assessors…independent of the study	• Modified Rankin Scale score, which must …; assessors…independent (not involved with the care of study subjects).	
11.10.4 12-Month (365±45 Days) Follow-up	• Modified Rankin Scale score, which must …; assessors…independent of the study • Neurological physical examination, which must …assessors should be independent of the study • NIH Stroke Scale (NIHSS), which must …; assessors…independent of the study • Rotational x-ray … Operations). It must be ...	• Modified Rankin Scale score, which must …; assessors…independent (not involved with the care of study subjects). • Neurological physical examination required in the main trial cohort, which must ... fellow (see Table 11.1-1); assessors should be independent (not involved with the care of study subjects). A neurological physical examination is not required in the extended trial cohort (see Table 11.1-2). • NIH Stroke Scale (NIHSS), which must …; assessors…independent (not involved with the care of study subjects). • Rotational x-ray angiography … Operations) is required in the main trial cohort. It must be ... Rotational x-ray angiography is not required in the extended trial cohort.	
11.10.5 Annual Follow-up (±45 Days)	• Modified Rankin Scale score, which must …; assessors…independent of the study • Rotational x-ray … Operations). It must be …. • Complete serious adverse event (SAE, SADE, USADE, ADE and CEC events)…	• Modified Rankin Scale score, which must …; assessors…independent (not involved with the care of study subjects). • Rotational x-ray angiography … Operations) is required in the main trial cohort. It must be… Rotational x- ray angiography is not required in the extended trial cohort. • Complete serious adverse event (SAE, SADE, USADE, and CEC events)…	

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11.10.6 Management of Missed…	Missed …as such on a regular basis in accordance with BSC standard operating procedures.	Missed …as such by the sponsor or designee on a regular basis in accordance with the applicable standard operating procedures.	Clarification
12.1.1.1 Primary Device Performance Endpoint	Two interim … . on the full enrolled cohort… This corresponds… gradient being <18 mm Hg.	Two interim … on the main trial cohort (N=120). … This corresponds… gradient being <18 mm Hg.	Clarification regarding main trial cohort analysis.
12.1.1.2 Sample Size-Primary Device Performance Endpoint	Two … A final analysis will be carried out on the full enrolled cohort.	Two … A final analysis will be carried out on the fully enrolled main trial cohort	Clarification that the primary device performance endpoint analysis is carried out on the main trial cohort.
12.1.1.3 Primary Safety Endpoint	Descriptive statistics … post implant procedure).	Subsequent to the enrollment of the main trial cohort for device performance assessment (see Section 12.1.1.2), up to 130 more subjects will be enrolled in the extended trial cohort to perform a statistically powered assessment of the primary safety endpoint. The null and alternative hypotheses for the primary safety endpoint are as follows. H_0: $\text{Mortality}_{30D} \geq PG$ H_1: $\text{Mortality}_{30D} < PG$ where Mortality_{30D} is the 30-day all-cause mortality rate for the Lotus Valve and PG is the performance goal. Testing will be done for the primary safety endpoint as described in the statistical analysis plan. A one-sample *z*-test will be used, the *z*-test statistic is $z = \frac{P_{30D} - PG}{s_p}$, where P_{30D} is the sample 30-day all-cause mortality rate,	Add statistically powered analysis of the primary safety endpoint.

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		PG is the performance goal, $s_p = \sqrt{\frac{P_{30D}(1-P_{30D})}{N}}$ is the sample standard error, N is the sample size. A sensitivity analysis (tipping-point analysis) will be performed to assess the impact of subjects with inadequate follow-up (i.e., missing data) on the primary safety endpoint and to assess the robustness of the conclusion of the primary analysis. The sample size calculation for the primary safety endpoint is based on the following assumptions. • Expected 30-day all-cause mortality rate = 9.8% • Performance goal (PG) = 16 % (expected rate of 9.8% + testing margin of 6.2%) • Test significance level (α) = 0.025 (1-sided) • Power ($1 - \beta$) = 80% • Expected rate of attrition = 2% If the *P* value from the one-sample *z*-test is <0.025, it will be concluded that the primary safety endpoint for the Lotus Valve is less than the PG. This corresponds to the one-sided upper 97.5% confidence bound of the observed 30-day mortality rate being <16 %. The expected rate of 9.8% for 30-day all-cause mortality is based on a literature review. [8-13,16-18,20,22,24-28,32-37] Given the above assumptions, 233 subjects will be required. In order to account for a 5% expected rate of attrition, a total of 250 subjects is required for the planned hypothesis testing.	

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Section Modified	**Text as Written in REPRISE II Protocol Version AE**	**Text as Written in REPRISE II Protocol Version AF**	**Justification for Modification**
12.2.1 Analysis Sets 12.2.2 Control of Systematic…	The primary analysis population for the primary device performance endpoint will be the subject population implanted with the Lotus Valve. Outcomes will be compared to a performance goal (PG). All subjects who have met the inclusion/exclusion criteria, (including a positive recommendation from the CRC) and have signed the informed consent form will be eligible for enrollment in the study. The investigator's assessment of TTE measurements before device placement will determine subject eligibility for the study.	The primary analysis population for the primary device performance endpoint will be the subject population implanted with the Lotus Valve (as-treated subject population). All subjects who have met the inclusion/exclusion criteria, received a positive recommendation from the CRC, and signed the informed consent form will be eligible for enrollment in the study. The center's heart team assessments and imaging measurements before device placement will contribute to the determination of subject eligibility for the study.	Clarification
12.3.2 Interim Analyses	… the first 40 and 60 enrolled subjects… carried out on the full enrolled cohort. The Pocock alpha…respectively.	…the first 40 and 60 enrolled subjects… The final analysis of the primary device performance endpoint will be conducted on the fully enrolled main trial subject cohort (N=120). The Pocock alpha … respectively.	Clarification of analyses on the main trial cohort
13.3.2 CT and…	An independent Core Laboratory will centrally assess all of the CT and rotational X-ray data…	An independent Core Laboratory will centrally assess all of the CT and rotational X-ray angiography data…	Clarification
16. Device Accountability	The principal investigator …verified by BSC personnel. • Identification of….Lot numbers)	The principal investigator …verified by Boston Scientific personnel or its designee. • Identification of….Lot numbers, valve size)	
17.1 Statement…	The REPRISE II study will be conducted in accordance with the relevant parts of the International …Helsinki; the International Conference on Harmonisation…	The REPRISE II study will be conducted in accordance with the International Helsinki; the relevant parts of the International Conference on Harmonisation…	
17.4 Sponsor Responsibilities	All information and data sent to BSC concerning subjects …. Only authorized BSC personnel, or a BSC representative will have access…	All information and data sent to Boston Scientific and its authorized designee concerning subjects …. Only authorized Boston Scientific personnel, representative or designee will have access… **Note:** Boston Scientific may utilize a contract research organization (CRO) or other contractors to act as its representative for carrying out designated tasks.	

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17.4.1 Training	In compliance with … includes the following requirements for implanting investigators.	In compliance with … includes the following elements for implanting investigators.	
18 Monitoring	Monitoring will be performed during the study …to assess	Monitoring will be performed during the study according to the monitoring plan to assess…	
19.3.2 Potential Benefit…	Potential benefits… the following. • Accurate… • Device is minimally obstructive to the blood flow through the annulus during delivery because there is no balloon or other obstructive device required for deployment • Reduced incidence…	Potential benefits… the following. • Pre-loaded delivery system minimizing time required and potential issues with preparing the device • Accurate… • 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 or obviated need for valve-in-valve repeat intervention • Reduced incidence…	
21.1 Definitions and Classifications	…the complications and AEs must be reported as AEs or SAEs if they meet the protocol-specified definitions. However, the original elective/planned hospitalization(s) itself should not be reported as an SAE. Any AE experienced by the study subject after enrollment, whether… Based on the VARC… following. • Mortality… • Vascular complications: major and minor •Repeat procedure for valve-related dysfunction (surgical or interventional therapy) • Hospitalization…	…the complications and AEs must be reported as AEs or SAEs if they meet the protocol-specified definitions. Any AE experienced by the study subject beginning from the time of Lotus Introducer sheath insertion, whether… Based on the VARC… following. • Mortality… • Neurologic event: disabling or non-disabling stroke, and TIAs • Myocardial infarction… • Vascular complications: major and minor •Repeat procedure for valve-related dysfunction (surgical or interventional therapy) • Hospitalization…	Sentence removed to avoid confusion. Clarification
21.3 Investigator Reporting	Table 21.3-1. Investigator Reporting Requirements USADE Complete AE electronic case report form (eCRF) page with	Table 21.3-1. Investigator Reporting Requirements USADE Complete AE electronic case report form (eCRF) page with	Simplification and clarification of requirements

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Requirements	all available new and updated information • Within 1 business day of first becoming aware of the event • Terminating at the end of the study ****** <u>SAE/SADE</u> Complete AE eCRF page with all available new and updated information • Within 2 business days of first becoming aware of the event or as per local/regional regulations • Reporting required through the end of the study ****** <u>AE</u> Complete AE eCRF page, which contains such information as date of AE, treatment of AE resolution, assessment of seriousness and relationship to the device • No later than 10 working days after becoming aware of the information • Reporting required through 12 months ****** <u>Device Deficiencies, Failures, Malfunctions, and Product Nonconformities</u> Complete applicable CRF fields/pages with all available new and updated information. • Within 1 business day of first becoming aware of the event and as per local/regional regulations • Reporting required through the end of the study	all available new and updated information • Within 1 business day of first becoming aware of the event • Beginning from time of Lotus Introducer sheath insertion for all subjects • Terminating at the end of the study Provide copies of all relevant source documents requested by Boston Scientific • As soon as possible after reporting the event ****** <u>SAE/SADE</u> Complete AE eCRF page with all available new and updated information • Within 2 business days of first becoming aware of the event or as per local/regional regulations • Beginning from time of Lotus Introducer sheath insertion for all subjects • Reporting required through the end of the study ****** <u>AE</u> Complete AE eCRF page, which contains such information as date of AE, treatment of AE resolution, assessment of seriousness and relationship to the device • Review with CRA during next monitoring visit • Beginning from time of Lotus Introducer sheath insertion for all subjects • Reporting required through 12 months ****** <u>Device Deficiencies, Failures, Malfunctions, and Product Nonconformities</u> Complete applicable CRF fields/pages with all available new and updated information.	

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Section Modified	**Text as Written in REPRISE II Protocol Version AE**	**Text as Written in REPRISE II Protocol Version AF**	**Justification for Modification**
		• Within 1 business day of first becoming aware of the event and as per local/regional regulations • Beginning from time of Lotus Introducer sheath insertion for all subjects • Reporting required through the end of the study	
26.2 Definitions DEVICE SUCCESS	Device Success as defined by VARC [44] post-implant procedure. • Absence of procedural mortality…	Device Success as defined by VARC post-implant procedure. VARC 1 [44] • Successful vascular access, delivery and deployment of the device and successful retrieval of the delivery system • Correct position of the device in the proper anatomical location • Intended performance of the prosthetic heart valve (aortic valve area >1.2 cm2 and mean aortic valve gradient <20 mmHg or peak velocity <3 m/s, without moderate or severe prosthetic valve aortic regurgitation) • Only one valve implanted in the proper anatomical location VARC 2 [48] • Absence of procedural mortality…	Indicate both VARC 1 and VARC 2 definitions here to be able to pool REPRISE II outcomes with data from REPRISE I (which used VARC 1 definitions) and to compare with published data using VARC 1 definitions.