Edwards

PARTNER 3 Trial – Mitral Valve in Valve

A Prospective, Single-Arm, Multicenter Study to Investigate the Safety and Effectiveness of SAPIEN 3 Transcatheter Heart Valve Implantation in Patients with a Failing Mitral Bioprosthetic Valve

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May 8, 2020

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Study Sponsor:

Edwards Lifesciences LLC
One Edwards Way
Irvine, CA 92614
USA

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PROTOCOL SYNOPSIS

Title	A prospective, single-arm, multicenter study to investigate the safety and effectiveness of SAPIEN 3 transcatheter heart valve (THV) implantation in patients with a failing mitral bioprosthetic valve
Purpose	To assess the safety and effectiveness of the SAPIEN 3 THV in patients with a failing mitral bioprosthetic valve
Study Device	Edwards SAPIEN 3 THV system with the associated delivery systems
Control	Not applicable
Study Design	Prospective, single-arm, multicenter study
Patient Population	Patients with symptomatic heart disease due to a failing bioprosthetic mitral valve (stenosed, insufficient, or combined) who are judged by a heart team, including a cardiac surgeon, to be at intermediate risk for open surgical therapy (i.e., predicted risk of surgical mortality ≥ 3% and < 8% at 30 days, based on the Society of Thoracic Surgeons [STS] risk score and other clinical co-morbidities unmeasured by the STS risk calculator).
Sample Size	A total of 50 patients who undergo the procedure
Study Sites	Up to 15 US sites and up to 5 sites outside the US will participate
Visit Schedule	Screening/Baseline, Procedure, Discharge, 30 days, 6 months, and annually through 10 years
Primary Endpoint	Safety and Effectiveness: Non-hierarchical composite endpoint of all-cause mortality and stroke at 1-year post-procedure
Secondary Endpoints for Labeling	1. New York Heart Association (NYHA) Functional Class at 30 days 2. Kansas City Cardiomyopathy Questionnaire (KCCQ) at 30 days 3. Mitral regurgitation (MR) at 30 days 4. Pulmonary artery systolic pressure at 30 days
Additional Secondary Endpoints	1. Procedure success defined as absence of procedural mortality AND correct positioning of a single prosthetic heart valve into the proper anatomical location 2. Mortality (all cause & cardiovascular) at 30 days and 1 year 3. Stroke (disabling and nondisabling) at 30 days and 1 year 4. Vascular complications (major) at 30 days and 1 year 5. Bleeding complications (life-threatening, disabling, or major) at 30 days and 1 year 6. Myocardial infarction requiring intervention at 30 days and 1 year 7. Acute kidney injury (AKI) at 30 days 8. Requirement for renal replacement therapy at 1 year 9. New permanent pacemaker implantation resulting from new or worsened conduction disturbances at 30 days and 1 year 10. NYHA Functional Class at 1 year 11. Hemodynamic function: mean and peak gradient at 30 days, years 1 through 5, year 7 and year 10

12. Mitral valvular regurgitation (paravalvular & central) at years 1 through 5, year 7 and year 10
13. New onset atrial fibrillation at 30 days and 1 year
14. Rehospitalization (valve-related or procedure related and including congestive heart failure [CHF]) at 30 days, 1 year, and annually
15. Index hospitalization days, intensive care unit (ICU) days, and discharge location
16. Structural valve deterioration (SVD) at years 1 through 5, year 7 and year 10
17. Days alive and out of hospital at 1 year
18. Six-minute walk test (6MWT) at 1 year
19. Heath status as evaluated by Quality of Life (QoL) questionnaires
    a. KCCQ at 1 year
    b. EQ-5D-5L at 30 days and 1 year
    c. SF-36 at 30 days and 1 year

Inclusion Criteria

Patients for this study must meet all of the following inclusion criteria:

1. Failing surgically implanted bioprosthetic valve in the mitral position demonstrating ≥ moderate stenosis and/or ≥ moderate insufficiency.
2. Surgical bioprosthetic valve with a true internal diameter (True ID) of 16.5 mm to 28.5 mm.
3. NYHA Functional Class ≥ II.
4. Heart Team agrees the patient is intermediate risk (i.e. STS score of ≥ 3 and <8). The Heart Team evaluation should include risk calculators such as the STS as well as overall clinical status and comorbidities not fully addressed by the STS risk score (verified during the case review process).
5. Heart Team agrees valve implantation will likely benefit the patient.
6. The study patient has been informed of the nature of the study, agrees to its provisions and has provided written informed consent as approved by the Institutional Review Board (IRB) / Ethics Committee (EC) of the respective clinical site.

Exclusion Criteria

Patients will be excluded from the study if any of the following conditions are present:

1. Index valve has ≥ mild paravalvular regurgitation where the surgical bioprosthesis is not securely fixed in the native annulus or is not structurally intact as determined by transesophageal echocardiography (TEE).
2. Surgical or transcatheter aortic valve placed so that extension into left ventricular outflow tract (LVOT) may impinge on the mitral implant.
3. Known residual mean gradient >10 mmHg at the end of the index procedure for implantation of the original surgical valve.
4. Severe right ventricle (RV) dysfunction.
5. Anatomical characteristics that would preclude safe access to the apex (transapical).
6. Severe regurgitation or stenosis of any other valve.
7. Severe lung disease (FEV1 < 50% predicted) or currently on home oxygen.

8. Severe pulmonary hypertension (e.g., PA systolic pressure ≥ 2/3 systemic pressure)
9. Anatomical characteristics that would increase risk of LVOT obstruction (e.g., aortomitral angle, LVOT size, etc.)
10. Evidence of an acute myocardial infarction ≤ 1 month (30 days) before enrollment.
11. Any therapeutic invasive cardiac procedure resulting in a permanent implant that is performed within 30 days prior to the index procedure. Implantation of a permanent pacemaker (PPM) or implantable cardioverter defibrillator (ICD) is not considered an exclusion.
12. Patients with planned concomitant surgical or transcatheter ablation for atrial fibrillation.
13. Leukopenia (white blood count < 3000 cell/mL), anemia (hemoglobin < 9 g/dL), thrombocytopenia (blood platelet count < 50,000 cell/mL), history of bleeding diathesis or coagulopathy, or hypercoagulable states.
14. Untreated clinically significant coronary artery disease requiring revascularization.
15. Hemodynamic or respiratory instability requiring inotropic support, mechanical ventilation, or mechanical heart assistance within 30 days of enrollment.
16. Emergency interventional/surgical procedures within one month (30 days) prior to the procedure.
17. Any planned surgical, percutaneous coronary, or peripheral procedure to be performed within the 30-day follow-up from the procedure.
18. Hypertrophic cardiomyopathy with obstruction (HOCM).
19. Left ventricular ejection fraction (LVEF) < 30%.
20. Cardiac imaging evidence of intracardiac mass, thrombus, or vegetation.
21. Inability to tolerate or condition precluding treatment with antithrombotic/anticoagulation therapy during or after the valve implant procedure.
22. Absolute contraindications or allergy to iodinated contrast that cannot be adequately treated with premedication.
23. Stroke or transient ischemic attack (TIA) within 90 days of enrollment.
24. Symptomatic carotid or vertebral artery disease or successful treatment of carotid stenosis within 30 days of enrollment.
25. Renal insufficiency (eGFR < 30 ml/min per the Cockcroft-Gault formula) and/or renal replacement therapy at the time of screening.
26. Active bacterial endocarditis within 6 months (180 days) of the procedure.
27. Patient refuses blood products.
28. Estimated life expectancy < 24 months.
29. Currently participating in an investigational drug or another device study. Note: Clinical trials requiring extended follow-up for products that were investigational, but have since become commercially available, are not considered investigational trials.

	30. Positive urine or serum pregnancy test in female subjects of childbearing potential.
Statistical Analysis	Statistical comparison against baseline will be performed for selected secondary endpoints. All other data will be summarized descriptively.
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INVESTIGATOR SIGNATURE PAGE

I have read this protocol and agree to adhere to its requirements. I will ensure that the study is conducted in compliance with the protocol, Good Clinical Practice, Declaration of Helsinki, and all applicable regulatory requirements.

_____

Investigative Site Name

_____

Site Principal Investigator Name (print)

_____ _____

Site Principal Investigator Signature Date

1 INTRODUCTION

Since the initial implantations in 2002, transcatheter heart valve (THV) replacement has evolved into a recognized alternative therapy to open heart surgery for inoperable and high risk patients with severe native aortic valve stenosis. More recently, patients with a previously implanted failing aortic and mitral surgical bioprostheses have also been identified as additional patient populations that requires mediation of stenotic, regurgitant, or combined prosthetic lesions. The ability to perform a reoperative valve replacement on the beating heart without the need for a full median sternotomy or use of the heart-lung machine is an equally desirable option for patients with a failing bioprosthesis in the mitral position and requires further study.

Mitral valve disease requiring intervention is manifested by stenosis and/or regurgitation. Mitral stenosis (MS) is most commonly associated with rheumatic heart disease resulting in progressive thickening and scarring of the mitral valve structures and narrowing of the mitral valve opening. The incidence of rheumatic fever has dropped dramatically in developed countries is rarely seen in the United States. Most cases of MS are in patients who have emigrated from countries where rheumatic fever is still endemic.[1] By nature of the disease, affected individuals are typically over the age of 65 years[2], the majority of who are Medicare beneficiaries in the United States (US). Mitral regurgitation (MR) can be caused by rheumatic disease or infections, mitral valve prolapse or myocardial ischemia and accounts for the majority of mitral valve interventions.

For MS, the definitive treatments are balloon valvuloplasty or in severe cases, valve replacement. Mitral valve repair with an annuloplasty device is the treatment of choice for MR. When this is not possible, a mitral valve replacement is performed with the preference for a bioprosthesis in the elderly. Mitral valve replacement with a stented bioprosthesis instead of a mechanical prosthesis is often chosen for patients in normal sinus rhythm, but also in those with the need to avoid oral anticoagulation such as patients with a history of gastrointestinal bleeding, concomitant coronary artery disease, high-risk occupations or in females planning for children.

Biological heart valve substitutes became available in the 1960s to replace severely stenotic native aortic and mitral valves and in contemporary clinical practice are the valves of choice for surgical therapy in the older patient population[3]. Bioprostheses are recognized for their reduced risk of thromboembolic events, avoidance of anticoagulation and good hemodynamic performance. The most commonly used biological prostheses are stented heterografts (xenografts) made of bovine pericardium or porcine aortic valves that are mounted on a metal alloy or polymer frame. The cloth-covered frame includes a sewing ring to aide in fixation of the device to the annular remnant of the resected native aortic valve or atrial aspect mitral valve orifice.

The last 60 years of bioprosthetic valve development and manufacturing have seen advances and improvements in tissue preservation and fixation, calcification mitigation processes and valve design that have streamlined procedures and extended the durability of these devices. Acceptable intermediate- (5 years), long-term (15 years) and very long-term results (25 years) have been observed and recently published in patients receiving a mitral xenograft at the age of 68 years or older. [4,5,6] Between 1999 and 2002, the United States STS database reported an

increase in the implantation of bioprosthetic valves from 50% to 65%.[7,8] Mitral valve repair procedures reportedly increased from 18.9% in 1998 to 45.8% in 2005. During the same period however, mitral valve replacements decreased[3].

Over time various cellular mechanisms, such as lipid-mediated inflammation, immune response and dysfunctional phosphocalcific metabolism can contribute to calcification and intrinsic changes to the prosthetic tissue that result in leaflet dysfunction and deterioration.[9] It has been shown that calcification begins in the areas of greatest stress to the leaflets mostly commonly at the commissures and in the basal areas of the leaflets. Thrombus and vegetation's related to endocarditis can also cause extrinsic calcification on the leaflets and progressive collagen deterioration of the tissue can result in design-related leaflet tearing requiring urgent reoperation.

This primary tissue failure is also referred to as structural valve deterioration (SVD) and is seen in both stented and stentless pericardial and porcine devices in the aortic and mitral positions[10]. SVD is also the dominant complication in mitral valve bioprostheses with an onset that is often recognized earlier than with aortic devices. This is thought to be due to the higher closing pressures during systole against the mitral leaflets when compared to lower diastolic pressures closing the aortic valve. In mitral valve patients SVD changes may be seen as early as 4-5 years and by 10 years may average 30%. By 15 years postoperatively, the actuarial freedom from mitral bioprosthetic primary tissue failure has ranged from 35 to 71%.[11] Recent case studies report SVD requiring explant in 2 Perimount mitral bioprostheses after 16 and 22 years respectively[12, 13]. As with aortic valves, deterioration is age related with SVD occurrence higher in younger patients.

Treatment options for patients with a failing surgical bioprosthetic valve in the mitral position are similar to those for patients with native valve mitral stenosis with regurgitation including; percutaneous balloon valvuloplasty for temporary relief of stenosis, reoperative surgical replacement of the degenerated device, the implantation of a transcatheter valve within the surgical valve (VinSV) or palliative medical therapy without an obstruction-relieving procedure.

Inoue published the first clinical report of using balloon valvuloplasty to manage mitral stenosis[14]. The use of balloon valvuloplasty in patients with failing aortic and mitral bioprosthetic devices was first described in the late 1980's and by the early 1990´s was reported with varying degrees of success; although technically possible it has been associated with surgical valve tissue disruption resulting in severe aortic regurgitation[15] and/or embolization of friable calcific deposits or thrombotic material[16]. It is currently recommended as a palliative therapy in patients with failing bioprosthetic heart valves.

When patients become symptomatic, a prosthetic valve replacement is necessary. Chan and colleagues[17] examined the need for reoperation according to age at implant in 3975 patients who had undergone a primary aortic valve replacement (AVR, n =3152) or mitral valve replacement (MVR, n=823) with a bioprosthetic valve between 1976 and 2010. In MVR, 59% of patients received a Hancock II porcine valve and 29% an Ionescu-Shiley pericardial prosthesis. A subsequent mitral valve reoperation was reported in 144 patients with 23 less than 40 years of age, 91 between 40 and 60 years and in 30 patients more than 60 years of age. At 15 years the

freedom from reoperation was more than 80% for patients older than 65 years. The time to MV reoperation was 8.1 years in patients less than 40 years and 10.1 years in patients between 40 and 60 years. In both the AVR and MVR group the median interval to reoperation was not reached in patients older than age 60 indicating that at no time point did 50% of these patients undergo reoperation. Univariable risk factors for AVR and MVR reoperation with a contemporary bioprosthesis were age and concomitant CABG surgery. The authors observed in the older patient population (>60 years) that the 15-year freedom from reoperation 62% for MVR.

In patients requiring a conventional reoperation for a failing aortic or mitral bioprosthetic heart valve the primary goal is to minimize and avoid morbidity and mortality. Reoperative procedures in these patients are technically possible but often challenging as many patients have not been under regular medical care and observation and are referred late, often presenting in advanced age and poor functional condition with congestive heart failure, compromised hemodynamics and multiple organ comorbidities. The accompanying comorbidities can significantly affect the reoperative risk of mortality and has been reported as high as 20%[18-20] . Emergency reoperation carries an even higher mortality rate with reports between 22.6% and 44%[21,22].

Table 1 shows early mortality rates of reoperative valve surgery in biological valve series with more than 100 patients ranging from 6.5% to 13.8%.

Table 1. Early Mortality in Reoperative Valve Surgery

Series	Time Period	Patients	Valve Position	Early Mortality
Mazzucco et al, 1993 [23]	1970-1990	221	Mitral	10.4%
Akins et al, 1998 [24]	1985-1997	400	Aortic & Mitral	7.8%
Yamak et al, 1999 [25]	1986-1996	261	Mitral	7.7%
Caus et al, 1999 [26]	1978-1998	524	Aortic, Mitral & Tricuspid	8.0%
Dalrymple-Hay et al, 2002 [27]	1980-1999	259	Aortic & Mitral	6.5%
Jamieson et al, 2003 [28]	1975-1999	463	Mitral	7.1%
Balsam et al. 2010 [29] *Hospital mortality	1992-2007	363	Aortic & Mitral	13.8%*

The" valve-in-surgical valve" concept (THV in SV) was first reported in failed conventional biological valves with the insertion of mechanical valve substitutes in the early 1990´s.[30 33] The authors describe the challenges, difficulties and resulting complications associated with the removal of bioprosthetic devices that require replacement several years after initial implantation. The struts of mitral bioprostheses are often buried within the ventricular myocardium or, in the aortic position, are fused with the wall of the aortic root where there is also concern about adjacent structures such as the coronary ostia, underlying vessels, the His bundle and interventricular septum. Already at that time, caution was expressed about having devices of the right diameter to fit into the retained sewing rings and not leave the patient with residual stenoses.

THV-in-SV procedures experimentally examined in animals at the Heart Center in Leipzig, Germany were published in 2007[34]. Wenaweser and colleagues[35] in Switzerland reported the first human THV-in-SV in a degenerated Mitroflow pericardial valve (Sorin Group, Vancouver, BC, Canada) with a Medtronic CoreValve THV (Irvine, California USA) in 2007. Walther and colleagues[36] followed in 2008 with the first Edwards SAPIEN implant within an Edwards PERIMOUNT pericardial prosthesis.

Paradis and colleagues reviewed 9 case series papers published between 2011 and 2015 and presented a state-of-the-art review of transcatheter valve treatment for aortic and mitral surgical valve dysfunction[9]. Included in the review are 77 mitral valve-in-valve patients and 36 mitral valve-in-ring patients. The mean age of these patients was 72 years with very high mean surgical risk scores (STS = 13.8% and logistic EuroSCORE =40%). A SAPIEN XT THV was used in 83% of cases and a Medtronic Melody device in 12% of cases. The transapical approach was the preferred access route in 64% of cases and the transseptal approach in 36% of cases. Implantation success was 94.5% and the 30-day mortality rate was 8.2%. No LVOT obstruction was reported in the valve-in-valve cohorts.

Results from the VIVID registry presented at the 2015 EuroPCR in Paris, France were also available in the review and reported on 349 patients with a mitral valve-in-valve procedure and 88 patients with a valve-in-ring implantation (mean age 72 years, 60% female, mean STS = 12.9%). The majority of these patients presented with regurgitation (45%) followed by stenosis (23%) and combined lesions (32%). Transapical access was used in 78.9%, transseptal access in 18.5% and direct left atrial access in 2.5% of patients. Transcatheter valve malpositioning was reported in 6.6% of patients and a LVOT obstruction in 2.6% of valve-in-valve cases. All-cause death at 30 days was reported in the valve-in-valve cohort at 7.7%, strokes were reported in 2.9% and mitral regurgitation was seen in 2.6% of patients. There were limited reports of late results including 93 patients and a mortality rate of 20.5% was reported after a mean follow-up of 14 months. Thrombosis was reported in 4 valve-in-valve patients, a valve migration requiring a second transapical valve-in-valve procedure 2 months post-procedure was seen and no cases of structural valve deterioration requiring intervention were reported.

The list of references is given in Appendix C. Abbreviations and definitions for the terms used in the protocol are given in Appendices A and B, respectively.

2 STUDY OBJECTIVE

To assess the safety and effectiveness of the SAPIEN 3 THV in patients with a failing mitral bioprosthetic valve.

3 STUDY DESIGN

This is a prospective, single-arm, multicenter study of SAPIEN 3 THV implantation in patients with a failing bioprosthetic mitral valve demonstrating stenosis and/or insufficiency.

4 ENROLLMENT

A total of 50 patients will undergo the procedure at up to 15 US sites and up to 5 sites outside the US. No site will be allowed to enroll more than 25% of patients.

5 STUDY DEVICES

The devices used in the study are commercially available devices and include the following:

Edwards SAPIEN 3 System

- Edwards SAPIEN 3 THV (20 mm, 23 mm, 26 mm and 29 mm sizes)
- Edwards Commander Delivery System for transseptal delivery
- Edwards Certitude Delivery System for transapical delivery
- Edwards eSheath Introducer Sheath Set
- Edwards Certitude Introducer Sheath Set
- Edwards Crimper

5.1 DEVICE DESCRIPTIONS

5.1.1 Edwards SAPIEN 3 THV

The SAPIEN 3 THV (**Figure 1**) is a catheter-delivered heart valve that combines a balloon expandable stent and bioprosthetic valve technology.

The device is comprised of a balloon-expandable, radiopaque, cobalt-chromium alloy frame, a trileaflet bovine pericardial tissue valve, a PET internal fabric skirt, and a PET outer skirt. The valve tissue is treated with Edwards ThermaFix process, packaged and terminally liquid sterilized in a buffered glutaraldehyde solution.

Figure 1. Edwards SAPIEN 3 Model 9600TFX

The SAPIEN 3 is available in 4 sizes. For SAPIEN 3 THV-in-surgical valve procedures, size recommendations for surgical bioprostheses with true internal diameters are shown in **Table 2**.

Table 2. Device Sizing for SAPIEN 3 THV in Surgical Bioprosthesis Procedures

Surgical Valve True Internal Diameter[1]	SAPIEN 3 Size
16.5-19.0 mm	20 mm
18.5-22 mm	23 mm

22-25 mm	26 mm
25-28.5 mm	29 mm

[1] Bapat V, Attia R, Thomas M. Effect of Valve Design on the Stent Internal Diameter of a Bioprosthetic Valve: A Concept of True Internal Diameter and Its Implications for the Valve-in-Valve Procedure. JACC: Cardiovascular Interventions. Vol. 7, No. 2 2014: 115-127.

Note: The dimensions of the failed bioprosthesis should be determined so that the appropriate THV size can be implanted; and is best determined by using computed tomography to perform the necessary measurements. Surgical valve 'True ID' may be smaller than the labeled valve size.

5.1.2 Edwards Delivery Systems

The Commander and Certitude Delivery Systems include:

- Loader
- Qualcrimp Accessory
- 2-piece Crimp Stopper

Commander Delivery System

The Edwards Commander Delivery System consists of a Flex Catheter to aid in valve alignment to the balloon, tracking and positioning of the THV. The delivery system includes a tapered tip to facilitate crossing of the aortic valve. The handle contains a Flex Wheel to control flexing of the Flex Catheter, and a Balloon Lock and Fine Adjustment Wheel to facilitate valve alignment and positioning of the valve within the aortic annulus. A stylet is included within the guidewire lumen of the delivery system. The Balloon Catheter has radiopaque Valve Alignment Markers defining the working length of the balloon. A radiopaque Center Marker in the balloon is provided to help with valve positioning. A radiopaque Triple Marker proximal to the balloon indicates the Flex Catheter position during deployment.

Certitude Delivery System

The Edwards Certitude Delivery System includes a handle with a Flex Wheel for articulation of the Balloon Catheter and a Loader. The loader allows for the delivery of the crimped THV through the hemostasis valves of the sheath. Three radiopaque indicators on the catheter shaft define the position on the balloon where the THV should be crimped and also provide visualization of the balloon. The THV is crimped between the two radiopaque shoulders on the distal and proximal ends of the balloon. A radiopaque Center Marker in the balloon is provided to help with valve positioning. An inflation and guidewire hub are housed in the handle assembly.

Loader

The loader is used to aid insertion of the delivery system into the sheath and may be removed to utilize the full working length of the inserted device.

Qualcrimp Accessory

The Qualcrimp crimping accessory (packaged with the delivery systems) is used during crimping of the THV and is intended to protect the SAPIEN 3 leaflets.

Crimper and 2-piece Crimp Stopper

The crimper reduces the diameter of the THV to mount it onto its delivery system. The crimper is comprised of a compression mechanism that is closed with a handle located on the housing. A 2-piece crimp stopper (packaged with the delivery systems) attaches to the crimper and is used to correctly crimp the THV.

5.1.3 Edwards eSheath Introducer Set

The Edwards eSheath introducer set contains two dilators and a sheath with hydrophilic coating, and a loader packaged with the Edwards Commander delivery system. The Edwards eSheath introducer set is indicated for the introduction and removal of devices used with the Edwards SAPIEN 3 THV.

5.1.4 Certitude Introducer Sheath Set

The Edwards Certitude introducer sheath set is intended for use with the Edwards Certitude delivery system for delivery of the SAPIEN 3 THV via TA/TAo access. The sheath contains a radiopaque maker for visualization of the sheath tip and non-radiopaque depth markings on the distal end of the body of the sheath. The proximal end of the sheath includes a flush tube and three hemostasis valves. An introducer is supplied with the sheath. The entire introducer is radiopaque.

The SAPIEN 3 THV, Commander Delivery System, Certitude Delivery System, and components will be used per their respective IFU and after training of physicians/site personnel has been achieved as determined by the study Sponsor. Further descriptions of these devices are provided in the respective IFUs.

6 STUDY ENDPOINTS

6.1 Primary Endpoint

Non-hierarchical composite endpoint of all-cause mortality and stroke at 1-year post-procedure.

6.2 Secondary Endpoints for Labeling

1. New York Heart Association (NYHA) Functional Class at 30 days
2. Kansas City Cardiomyopathy Questionnaire (KCCQ) at 30 days
3. Mitral regurgitation (MR) at 30 days
4. Pulmonary artery systolic pressure at 30 days

6.3 Additional Secondary Endpoints

1. Procedure success defined as absence of procedural mortality AND correct positioning of a single prosthetic heart valve into the proper anatomical location
2. Mortality (all cause & cardiovascular) at 30 days and 1 year
3. Stroke (disabling and nondisabling) at 30 days and 1 year
4. Vascular complications (major) at 30 days and 1 year
5. Bleeding complications (life-threatening, disabling, or major) at 30 days and 1 year
6. Myocardial infarction requiring intervention at 30 days and 1 year
7. Acute kidney injury (AKI) at 30 days
8. Requirement for renal replacement therapy at 1 year
9. New permanent pacemaker implantation resulting from new or worsened conduction disturbances at 30 days and 1 year
10. NYHA Functional Class at 1 year
11. Hemodynamic function: mean and peak gradient at 30 days, years 1 through 5, year 7 and year 10
12. Valvular regurgitation (paravalvular & central) at years 1 through 5, year 7 and year 10
13. New onset atrial fibrillation at 30 days and 1 year
14. Rehospitalization (valve-related or procedure related and including congestive heart failure [CHF]) at 30 days, 1 year, and annually
15. Index hospitalization days, intensive care unit (ICU) days, and discharge location
16. Structural valve deterioration (SVD) at years 1 through 5, year 7 and year 10
17. Days alive and out of hospital at 1 year

18. Six-minute walk test (6MWT) at 1 year
19. Health status as evaluated by Quality of Life (QoL) questionnaires
    - KCCQ at 1 year
    - EQ-5D-5L at 30 days and 1 year
    - SF-36 at 30 days and 1 year

7 STUDY POPULATION / PROPOSED INDICATION FOR USE

The Edwards SAPIEN 3 THV, Edwards Commander and Certitude delivery systems and accessories are indicated for use in patients with symptomatic heart disease due to a failing bioprosthetic mitral valve (stenosed, insufficient, or combined) who are judged by a heart team, including a cardiac surgeon, to be at intermediate risk for open surgical therapy (i.e., predicted risk of surgical mortality ≥ 3% and < 8% at 30 days, based on the Society of Thoracic Surgeons [STS] risk score and other clinical co-morbidities unmeasured by the STS risk calculator).

7.1 Inclusion Criteria

Patients must meet the following inclusion criteria:

1. Failing surgically implanted bioprosthetic valve in the mitral position demonstrating ≥ moderate stenosis and/or ≥ moderate insufficiency.
2. Surgical bioprosthetic valve with a true internal diameter (True ID) of 16.5 mm to 28.5 mm.
3. NYHA Functional Class ≥ II.
4. Heart Team agrees the patient is intermediate risk (i.e. STS score of ≥3 and < 8). The Heart Team evaluation should include risk calculators such as the STS as well as overall clinical status and comorbidities not fully addressed by the STS risk score (verified during the case review process).
5. Heart Team agrees valve implantation will likely benefit the patient.
6. The study patient has been informed of the nature of the study, agrees to its provisions and has provided written informed consent as approved by the Institutional Review Board (IRB) / Ethics Committee (EC) of the respective clinical site.

7.2 Exclusion Criteria

Patients will be excluded from the study if any of the following conditions are present:

1. Index valve has ≥ mild paravalvular regurgitation where the surgical bioprosthesis is not securely fixed in the native annulus or is not structurally intact as determined by transesophageal echocardiography (TEE).
2. Surgical or transcatheter aortic valve placed so that extension into left ventricular outflow tract (LVOT) that may impinge on the mitral implant.
3. Known residual mean gradient >10 mmHg at the end of the index procedure for implantation of the original surgical valve.
4. Severe right ventricle (RV) dysfunction.
5. Anatomical characteristics that would preclude safe access to the apex (transapical).
6. Severe regurgitation or stenosis of any other valve.
7. Severe lung disease (FEV1 < 50% predicted) or currently on home oxygen
8. Severe pulmonary hypertension (e.g., PA systolic pressure ≥ 2/3 systemic pressure)
9. Anatomical characteristics that would increase risk of LVOT obstruction (e.g., aortomitral angle, LVOT size, etc.).
10. Evidence of an acute myocardial infarction ≤ 1 month (30 days) before enrollment.
11. Any therapeutic invasive cardiac procedure resulting in a permanent implant that is performed within 30 days prior to the index procedure. Implantation of a permanent pacemaker (PPM) or implantable cardioverter defibrillator (ICD) is not considered an exclusion.
12. Patients with planned concomitant surgical or transcatheter ablation for atrial fibrillation.
13. Leukopenia (white blood count < 3000 cell/mL), anemia (hemoglobin < 9 g/dL), thrombocytopenia (blood platelet count < 50,000 cell/mL), history of bleeding diathesis or coagulopathy, or hypercoagulable states.
14. Untreated clinically significant coronary artery disease requiring revascularization.
15. Hemodynamic or respiratory instability requiring inotropic support, mechanical ventilation, or mechanical heart assistance within 30 days of enrollment.
16. Emergency intervention/surgical procedures within one month (30 days) prior to the procedure.
17. Any planned surgical, percutaneous coronary, or peripheral procedure to be performed within the 30-day follow-up from the procedure.
18. Hypertrophic cardiomyopathy with obstruction (HOCM).
19. Left ventricular ejection fraction (LVEF) < 30%.
20. Cardiac imaging evidence of intracardiac mass, thrombus, or vegetation.

21. Inability to tolerate or condition precluding treatment with antithrombotic/anticoagulation therapy during or after the valve implant procedure.
22. Absolute contraindications or allergy to iodinated contrast that cannot be adequately treated with premedication.
23. Stroke or transient ischemic attack (TIA) within 90 days of enrollment.
24. Symptomatic carotid or vertebral artery disease or successful treatment of carotid stenosis within 30 days of enrollment.
25. Renal insufficiency (eGFR < 30 ml/min per the Cockcroft-Gault formula) and/or renal replacement therapy at the time of screening.
26. Active bacterial endocarditis within 6 months (180 days) of the procedure.
27. Patient refuses blood products.
28. Estimated life expectancy < 24 months.
29. Currently participating in an investigational drug or another device study. Note: Clinical trials requiring extended follow-up for products that were investigational, but have since become commercially available, are not considered investigational trials.
30. Positive urine or serum pregnancy test in female subjects of childbearing potential.

8 STUDY PROCEDURES

8.1 Screening Period

The screening period is designed to obtain patient consent, determine patient eligibility for the study, and to submit the presentation for case review. The Screening Visit procedures will occur within the 30 days prior to the valve implant procedure, unless otherwise noted below. All patients that sign an informed consent will be entered into the electronic database (EDC) and be assigned a Subject ID. All assessments performed will be entered into EDC.

Patients that have signed the informed consent and do not meet the inclusion/exclusion criteria in Sections 7.1 and 7.2 will be considered a Screen Failure (SF). All assessments performed and the inclusion or exclusion criteria that was not met will be entered into EDC.

The patient status will be considered ‘Discontinued’ if the following occur during the screening period:

- The patient withdraws consent or expires prior to or after the Case Review
- The patient completes all of the screening procedures, including Case Review call, and Case Review is not approved

All assessments performed and the reason for patient discontinuation will be entered into EDC and the Exit form will be completed.

The following information will be collected during the screening period:

Consent:

- Patient informed consent completion (Section 8.1.1)

Operability:

- STS Risk Score

Other Assessments:

- Logistic EuroSCORE
- EuroSCORE II

Systems:

- Medical history, demographics and physical assessment
- Medications: anti-thrombotics/anticoagulants and HMG coA reductase inhibitors

Cardiopulmonary:

- Canadian Cardiovascular Society (CCS) status of angina
- 12-lead ECG
- NYHA Class
- Comprehensive transthoracic echocardiogram (TTE), including, but not limited to, assessment of mitral valve gradients (mean and peak), areas, indices, degree of regurgitation, left and/or right ventricle systolic function (global and segmental). Qualifying echocardiogram (echo) must be performed within 90 days prior to enrollment.
- Cardiac imaging (CT) with 3D reconstruction to verify failing prosthesis dimensions and to assess aortomitral annular angle and risk of LVOT obstruction. Qualifying cardiac imaging must be performed within 1 year prior to enrollment, unless clinically contraindicated.
- Assessment of severity of coronary artery disease (CAD) may be performed by CTA or coronary angiography. If CTA shows evidence or high likelihood of obstructive CAD or if the CTA is non-diagnostic, coronary angiography must be performed to assess the need for intervention. Qualifying CTA/coronary angiography must be performed within 1 year prior to the valve implant procedure.
- SYNTAX Score for significant native coronary artery disease (CAD)
- Pulmonary Function Test for patients with a history of lung disease

Neurological Assessments:

- Mini Mental State Examination (MMSE)
- National Institutes of Health Stroke Scale (NIHSS)
- Modified Rankin Scale (mRS)

Functional Assessments:

- Six Minute Walk Test (6MWT)
- Frailty Index (5 Meter Walk Test [5MWT], grip strength, Activities of Daily Living (ADL), and Albumin laboratory)
- Quality of Life Assessments
  - KCCQ
  - EQ-5D-5L
  - SF-36

Clinical Laboratory Tests:

- White Blood Count (WBC), Hemoglobin (Hgb), and platelet count
- Prothrombin time (PT) or International Normalized Ratio (INR)
- Creatinine
- Estimated glomerular filtration rate (eGFR)
- Albumin (as part of Frailty Index)
- Total Bilirubin
- Aspartate aminotransferase (AST)/Alanine aminotransaminase (ALT) (required for patients with chronic liver disease)
- B-type natriuretic peptide (BNP)
- Urine or serum pregnancy test for all females of childbearing potential

Eligibility Review:

- Case Review (Section 8.1.2)

8.1.1 Informed Consent

The study investigator(s) and support staff will approach patients with a failing surgically implanted bioprosthetic valve demonstrating moderate mitral stenosis and/or ≥ moderate insufficiency to assess their interest in participating in the study by providing them an overview of the study including the background, risks, benefits and study procedures. If patients are interested in participating in the study, the study patient will sign the IRB/EC approved informed consent form prior to any study specific procedures are performed. All patients consented should be entered into the study's EDC system.

8.1.2 Case Review

The Case Review Board is a select review committee comprised of Investigators who are participating in the trial. The role of the Case Review Board is to review submitted cases to determine if the patient is an appropriate candidate for the trial, with a focus on valve sizing, appropriate vascular access, and any relevant clinical factors impacting enrollment eligibility (e.g., risk of LVOT obstruction, etc.). Before a case is submitted for review, the site Principal Investigator and Heart Team will screen the patient for fundamental enrollment criteria. Once fully screened and deemed an appropriate candidate, the site will submit the case for review and approval consideration by the Case Review Board. Once a case is approved by the Case Review Board, the patient will be eligible for the implant procedure. The Sponsor will maintain a record of the case presentation and case approval notes.

8.2 Enrollment

Once all screening procedures have been completed, all inclusion/exclusion criteria have been confirmed and the Case Review has been completed and approved, the patient is considered to be enrolled in the study.

If the patient has been enrolled and the patient withdraws consent prior to the procedure start, the patient will be considered discontinued. All assessments performed and the reason for withdrawal will be entered into EDC and the Exit form will be completed.

8.3 Procedure (Day 0)

Every effort should be made to have the valve implant procedure performed within 14 days of enrollment. The date of the valve implant procedure is considered Day 0.

The valve implant procedure will be considered to have started when the first interventional access related puncture or skin incision occurs. Performance of TEE does not by itself constitute start of procedure.

Day 0 will be used to schedule all subsequent visits and calculate visit windows. Patients who receive the THV implant will continue in the study and complete the study through year 5 according to the visits and events described in Section 8.0 and Schedule of Procedures.

Day 0 valve implant procedure assessments will include the following:

Systems:

- Medications: anti-thrombotics/anticoagulants and HMG coA reductase inhibitors
- Adverse event assessment

Cardiopulmonary:

- Ventriculogram, transthoracic echocardiogram (TTE), or transesophageal echocardiogram (TEE) (TEE is required for transseptal procedures)

Procedural imaging (i.e., TEE and fluoroscopy) should be submitted to the Sponsor after the procedure.

If the valve implant is aborted (prior to or after the start of the valve implant procedure), the Day 0 visit may be re-scheduled if the patient continues to meet all inclusion/exclusion criteria.

8.3.1 Device Preparation

A detailed description of device preparation and required equipment is supplied in the IFU.

8.3.2 Procedure Recommendations

Table 3 outlines the recommended anticoagulation/antithrombotic regimen. The categories were developed by The PARTNER II Trial Patient and Procedure Management Steering Committee. There are no current validated guidelines in this specific study population, however, the literature was surveyed and used as guidance for the following proposed guidelines.[37]

NOTE: The CHAD score only applied to patients in AF and had not been validated in non-AF patient populations; therefore, the CHAD score reference was used as one among many guidelines to establish the risk stratification for intensity of anticoagulation regimen.

Table 3. Recommended Anticoagulation/Antithrombotic Regimen

Pre Valve Implant Procedure
• Aspirin 81-100 mg QD • Patients with BMS within one month or DES within 12 months should be continued on Clopidogrel/prasugrel prior to their implant procedure • Patients in atrial fibrillation on warfarin should be bridged with LMW or UF heparin prior to the implant procedure • Patients with persistent or paroxysmal atrial fibrillation, not on anti-coagulation, will not be required to have a TEE to rule out LA thrombus prior to implant procedure. If intra- procedural TEE during the implant reveals thrombus, the implant procedure will be aborted and delayed until the patient has been on warfarin or dabigatran for 30 days. Note: thrombus must be eliminated in order to proceed with the implant procedure. • In patients undergoing an implant procedure, clopidogrel loading with either 300 mg or 600 mg prior to the implant procedure is recommended in addition to ASA
Intraprocedural
• Heparin will be given to achieve/maintain ACT≥ 300 sec • The recommended dose of protamine after access closure is half of the full dose
Post-Procedure*
• Heparin use as a bridging agent to warfarin therapy is recommended until the INR stabilizes at 2 or greater, then continue with oral anticoagulants only • ASA 81 mg qd • In high risk patients, warfarin and Plavix is recommended when the INR ≥ 2; discontinue ASA • Warfarin for at least 6 months post-implant procedure (may be discontinued after 6 months if no AF) • Clopidogrel, 75 mg qd, if warfarin therapy has been discontinued
*Dual antiplatelet therapy (e.g., clopidogrel and aspirin) is not widely recommended, but may be considered on an individual basis if indicated for a given patient. The anticoagulant and antiplatelet regimen past the 6-month follow up visit will be determined at the Investigator's discretion.

AF=Atrial fibrillation.
Note: Any changes to antithrombotic/anticoagulation regimen from study visit to study visit will be noted on the Case Report Form (CRF) including reason for change.

8.3.3 Antibiotic Prophylaxis

Study patients should be prophylactically treated for endocarditis per the recommendations of the American Heart Association.

8.3.4 Contrast Media

Careful management of contrast media is required. Measurement of the contrast used will be captured in the CRF.

8.3.5 Radiation Precautions

Radiation precautions will be adhered to per institutional standards. Total procedural radiation exposure will be documented on the CRFs in accordance with institutional measures (i.e. total procedural fluoroscopy time, dosage, etc.).

Radiation exposure of 6-15 mSv is estimated for the Screening CT[38]. If a radiation induced skin injury is suspected, the Investigator should see the patient at an office visit and should arrange for appropriate follow-up care.

8.4 Post-Procedure

The post-implant procedure time period is defined as the 48 hours after the patient exits the cath lab/ operating room. Study patients will be continuously monitored clinically, hemodynamically, and electrocardiographically during catheterization for all local, systemic side effects and complications. After completion of the implant procedure, all study patients will be monitored per institution standard of care. Subsequent monitoring will also be continued according to institutional standard of care.

The following information will be collected during the Post-Procedure time period:

Systems:

- Medications: anti-thrombotics/anticoagulants and HMG coA reductase inhibitors
- Adverse event (AE) assessment

Cardiopulmonary:

- 12-lead ECG

Clinical Laboratory Tests:

- WBC, Hgb, and platelet count
- PT or INR
- Creatinine

Neurological assessments:

- NIHSS

8.5 Discharge

Discharge is the actual date and time the patient is discharged. For patients discharged within 48 hours of exiting the cath lab / operating room, it is not required to repeat tests collected during the Post-Procedure period that are also required for the discharge visit. If the patient was discharged over a weekend or holiday, the discharge assessments may be completed on the last weekday prior to discharge.

The following information will be collected for study patients within 24 hours of the date and time of discharge. The location the patient will be discharged to should be documented in the EDC form.

Systems:

- Physical assessment including weight, blood pressure, and heart rate

- Medications: anti-thrombotics/anticoagulants and HMG CoA reductase inhibitors
- AE assessment

Cardiopulmonary:

- NYHA Class
- TTE (per echo protocol)

Clinical Laboratory Tests:

- WBC, Hgb, and platelet count
- PT or INR
- Creatinine
- BNP

Neurological Assessments:

- NIHSS

8.6 Post-Procedure Follow Up Visits

8.6.1 30-Day Post-Procedure Visit

The 30-day post-procedure visit window will be calculated from the Day 0 valve implant date. The visit window is +7 days.

The following data will be collected for all study patients 30 days post-implant procedure.

Systems:

- Physical assessment including weight, blood pressure, and heart rate
- Medications: anti-thrombotics/anticoagulants and HMG CoA reductase inhibitors
- AE assessment

Cardiopulmonary:

- 12-lead ECG
- NYHA Class
- TTE (per echo protocol)

Neurological Assessments:

- MMSE
- NIHSS
- mRS

Functional Assessments:

- 6MWT
- Quality of Life Questionnaires
  - KCCQ
  - EQ-5D-5L
  - SF-36

Clinical Laboratory Tests:

- WBC, Hgb, and platelet count
- Creatinine
- BNP

8.6.2 6 -Month Post-Procedure Visit

The 6-month post-implant procedure visit window will be calculated from the Day 0 visit date. The visit window is +14 days.

The following data will be collected for all study patients 6 months post-valve implant procedure.

Systems:

- Physical assessment including weight, blood pressure, and heart rate
- Medications: anti-thrombotics/anticoagulants and HMG CoA reductase inhibitors
- AE assessment

Cardiopulmonary:

- NYHA Class

Functional Assessments:

- Quality of Life Questionnaires
  - KCCQ
  - EQ-5D-5L
  - SF-36

8.6.3 12-Month Post-Procedure Visit

The 12-month post-implant procedure visit window will be calculated from the Day 0 valve implant date. The visit window is +30 days.

The following data will be collected for all study patients 12-month post-implant procedure.

Systems:

- Physical assessment including weight and blood pressure
- Medications: anti-thrombotics/anticoagulants and HMG CoA reductase inhibitors
- AE assessment

Cardiopulmonary:

- 12-lead ECG
- NYHA Class
- TTE (per echo protocol)

Neurological Assessments:

- MMSE

Functional Assessments:

- 6MWT
- Quality of Life Questionnaires
  - KCCQ
  - EQ-5D-5L
  - SF-36

8.6.4 Years 2 through 10 Annual Post-Procedure Visit

The yearly post-implant procedure visit window will be calculated from the Day 0 valve implant date. The visit window is +45 days.

The following data will be collected for all study patient's years 2 through 10 annually post-implant procedure visit.

Systems:

- Physical assessment including weight, blood pressure, and heart rate
- Medications: anti-thrombotics/anticoagulants and HMG CoA reductase inhibitors
- AE assessment

Cardiopulmonary:

- NYHA Class
- TTE (years 2, 3, 4, 5, 7 and 10 only per echo protocol)

Functional Assessments:

- Quality of Life Questionnaire
  - KCCQ

- SF-36

8.7 Assessment for Leaflet Thrombosis

In the event that an increase in mean gradient of > 5mm Hg from post-procedure is identified OR the patient experiences any of the following AEs during the study, every effort should be made to obtain additional imaging (TEE or 4D CT, per local site practice) from the time of the event to determine the presence or absence of leaflet thrombosis. If unable to be obtained at the time of the event, imaging should be obtained at the patient's next scheduled follow up visit.

- Stroke
- TIA
- Other potential embolic event
- Worsening shortness of breath

8.8 Neurological Assessments

Every effort should be made to have a neurologist (or neurology fellow) perform the NIHSS and mRS assessments. If it is not possible to have the neurologist/fellow perform the assessments within the protocol-specified visit window, a certified study team member may perform the assessments.

Following the procedure, all subjects should be assessed to determine if there is evidence of neurological impairment. If symptoms of a stroke are suspected, the NIHSS should be performed. For all subjects diagnosed with a new stroke after the procedure start, a follow-up mRS assessment should be performed 90 days (± 30 days) after stroke onset to assess stroke disability (visit or phone assessment is acceptable). If the 90-day post-stroke assessment is scheduled to occur within 30 days of the next protocol-specified visit, the mRS does not need to be repeated.

8.9 Missed Visits

Site personnel should make all reasonable efforts to locate and communicate with the subject at each visit time point. For each missed visit, multiple attempts to contact the subject should be made and details recorded in the source documentation.

A patient is not considered lost to follow-up until the full 10 years of follow-up have elapsed.

8.10 Discontinuation after Entering the Procedure Room

Every patient should be encouraged to remain in the study until they have completed the protocol required follow-up period. If the patient discontinues prematurely from the study, the reason for discontinuation must be documented. All attempts should be made to have the patient come into the clinic for an Exit visit.

If the following situations occur, the patient status will be considered 'Discontinued':

- The patient has entered the cath lab or operating room (procedure room) and an inclusion or exclusion criteria failure has been found.
- The patient has entered the procedure room and expires prior to the start of the valve implant procedure.
- The patient expires after the procedure has started.
- The patient withdraws consent after the valve implant procedure and prior to the final study visit.
- The patient expires after the valve implant procedure and prior to the final study visit.

If the patient has a THV other than the SAPIEN 3 implanted, the patient status will be considered discontinued and the patient will be monitored through Day 30 or until any AEs occurring are resolved.

All assessments performed and the reason for discontinuation will be entered into EDC and Exit form completed.

8.11 Death Registries

In the event of a patient lost to follow-up or early withdrawal, Edwards may request the site to search the Social Security Death Index and/or other death registries. If patient death is confirmed, Edwards may request the site to obtain the death certificate.

Table 4. Schedule of Procedures

	Screening	Procedure (Implant)	Post-Procedure	Discharge	30D	6M	12M	2-10Y
Visit Window (days)	-30 [d]	0			+7	+14	+30	+45
Physical Assessment								
Informed Consent	X							
Medical History & Demographics	X							
Physical Assessment	X			X	X	X	X	X
CCS Angina	X							
NYHA Classification	X			X	X	X	X	X
MMSE	X				X		X	
STS Risk Score	X							
Logistic EuroSCORE	X							
EuroSCORE II	X							
SYNTAX Score	X							
Medications	X	X	X	X	X	X	X	X
Adverse Event Assessment		X	X	X	X	X	X	X
NIHSS [a]	X		X [b]	X [b]	X			
Modified Rankin Scale [a,c]	X				X			
6 Minute Walk Test	X				X		X	
Frailty Index [i]	X							
Laboratory Measurements								
WBC, Hgb, Platelet Count	X		X	X	X			
PT or INR	X		X	X				
eGFR	X							
Creatinine	X		X	X	X			
Albumin, Total Bilirubin	X							
AST/ALT [j]	X							
BNP	X			X	X			
Pregnancy test, if female of childbearing potential	X							
Non-Invasive Tests								
Pulmonary Function Test (PFT) [m]	X							
ECG	X		X		X		X	
Echocardiogram (TTE)	X [e]	X [h]		X	X		X	X [l]
Final Eligibility Review								
Case Review [g]	X							

	Screening	Procedure (Implant)	Post-Procedure	Discharge	30D	6M	12M	2-10Y
Visit Window (days)	-30 [d]	0			+7	+14	+30	+45
Invasive Tests								
3D Cardiac imaging (CT)	X [f]							
TEE or 4D CT					X [k]	X [k]	X [k]	X [k]
Valve implant procedure		X						
Assessment of CAD [n]	X							
Ventriculogram (mitral position) [h]		X						
Quality-of-Life Assessments								
KCCQ	X				X	X	X	X
EQ-5D-5L	X				X	X	X	
SF-36	X				X	X	X	X

a. Every effort should be made to have a neurologist (or neurology fellow) perform the NIHSS and mRS assessments. If it is not possible to have the neurologist/fellow perform the assessments within the protocol-specified visit window, a certified study team member may perform the assessments.

b. Following the procedure, all subjects should be assessed to determine if there is evidence of neurological impairment. If symptoms of a stroke are suspected, the NIHSS should be performed.

c. For all subjects diagnosed with a new stroke after the procedure start, a follow-up mRS assessment should be performed 90 days (± 30 days) after stroke onset to assess stroke disability (visit or phone assessment is acceptable). If the 90-day post-stroke assessment is scheduled to occur within 30 days of the next protocol-specified visit, the mRS does not need to be repeated.

d. Screening procedures will be completed within 30 days prior to the valve implant procedure unless otherwise noted.

e. Qualifying echocardiogram must have been performed within the 90 days prior to enrollment.

f. All patients will have cardiac imaging at the screening visit.

g. Case Review will be completed when all screening procedures have been completed, all inclusion/exclusion criteria have been fundamentally confirmed and the site is ready to present a case.

h. Ventriculogram, TTE, or TEE on date of valve implant procedure. TEE is required for transseptal procedures

i. Frailty Index includes activities of daily living (ADLs), 5 meter walk test (5MWT), grip strength, and albumin laboratory.

j. Only required for patients with chronic liver disease.

k. To determine the presence of leaflet thrombosis if clinically indicated and TEE or 4D CT imaging is unable to be obtained at the time of the event.

l. Echocardiograms to be obtained years 2, 3, 4, 5, 7 and 10.

m. Only for patients with a history of lung disease

n. Assessment of severity of coronary artery disease (CAD) may be performed by CTA or coronary angiography. If CTA shows evidence or high likelihood of obstructive CAD or if the CTA is non-diagnostic, coronary angiography must be performed to assess the need for intervention. Qualifying CTA/coronary angiography must be performed within 1 year prior to the valve implant procedure.

9 ADVERSE EVENTS

9.1 Definitions

Adverse Event

An Adverse Event (AE) is any untoward medical occurrence, unintended disease or injury or untoward clinical signs (including abnormal laboratory findings) in patients, users or other persons, whether or not related to the investigational medical device.

Adverse events may be volunteered by patients, elicited by the Investigator or designee, the CEC, safety team, monitoring team, or collected via observation by the Investigator. All AEs will be assessed by the Investigator who will determine whether or not the event is related to the device and/or implant procedure, and whether or not the event meets seriousness criteria. If it is determined that an AE has occurred, the investigator should obtain all the information required to complete the AE CRF.

In addition, patients will be advised to contact the investigator, and/or study coordinator if any significant adverse events occur between study visits.

All clinically significant AEs will be reported by the Investigator and reviewed by the Sponsor in compliance with applicable regulations as indicated below Section 9.2.

Serious Adverse Event

An Adverse Event is considered serious if the event:

- Leads to death;
- Leads to a serious deterioration in the health of the study patient that:
  - Results in life-threatening illness or injury;
  - Results in a permanent impairment of a body structure or a body function;
  - Requires inpatient hospitalization or prolongation of existing hospitalization;
  - Results in medical or surgical intervention to prevent permanent impairment to body structure or a body function;
- Led to fetal distress, fetal death or congenital abnormality or birth defect;
- Significant medical event.

Important medical events that do not meet the above criteria may still be considered an SAE if they seriously jeopardize the patient and require immediate medical or surgical intervention to prevent one of the aforementioned outcomes.

Death should not be recorded as an adverse event but should only be reflected as an outcome to another specific AE.

Anticipated Adverse Event

An anticipated adverse event is identified as a potential risk associated with the overall procedure or investigational device as stated in the IFU.

Unanticipated Adverse Device Effect

An Unanticipated Adverse Device Effect (UADE) is any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of patients.

The Investigator shall submit to the Sponsor and to the reviewing IRB/EC a report of any UADE occurring during an investigation as soon as possible, but in no event later than 10 days after the investigator first learns of the effect.

All adverse events assessed as UADEs must be followed until resolution or until a stable clinical endpoint is reached. All required treatments and outcomes of the UADE must be recorded.

Edwards will notify FDA as well as all participating clinical investigators and IRBs/ECs of all UADEs that occur during this study within 10 working days after becoming aware of the event. Investigators are responsible for reviewing information received about UADEs.

Device Malfunctions

A device malfunction is defined as the failure of a device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device. The intended performance of a device refers to the intended use for which the device is labeled or marketed.

Adverse Device Effect

An Adverse Device Effect (ADE) is an AE related to the use of a medical device.

NOTE 1: This includes any AE resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the medical device.

NOTE 2: This includes any event that is a result of a use error or intentional abnormal use of the medical device.

Serious Adverse Device Effect

A Serious Adverse Device Effect (SADE) is an ADE that has resulted in any of the consequences characteristic of a SAE.

Unanticipated Serious Adverse Device Effect

An Unanticipated Serious Adverse Device Effect (USADE) is defined as any SADE which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report or IFU.

Device Deficiency

A device deficiency is defined as an inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error or inadequacy in the information supplied by the manufacturer.

A malfunction or deterioration is defined as the failure of a device to perform in accordance with its intended purpose when used in accordance with the manufacturer´s instructions. The intended performance of a device refers to the intended use for which the device is labeled or marketed.

Reporting conventions for device deficiencies that could result in an SAE are the same as those for an actual SAE.

9.2 Causality of AEs

For each AE, the Investigator will determine whether the event is related to the device and/or the implant procedure, and whether the event meets the definition of a SAE.

The causal relationship of the event to the device and the implant procedure will be categorized as follows:

- **Not Related:** There is no relationship between the event and the device or procedure
- **Unlikely Related**: The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause
- **Possibly Related:** There is a possibility of relationship between the event and the device or procedure (temporal sequence; no contradicting evidence)
- **Related:** The event is related or most likely associated with the device or procedure (relevant temporal sequence; event abates upon device application completion/removal; no other reasonable explanation)

9.3 AE Reporting Requirements

All relevant AEs will be captured from the time of enrollment until the study patient’s participation has ended (i.e. completion of study or withdrawal of consent).

Adverse events must be followed until resolution, stabilization or study completion. The AE CRFs should be completed promptly:

US site reporting timelines: All AEs should be reported within 7 business days of becoming aware of the event. Device malfunctions should be reported within 10 days of the site becoming aware of the event.

OUS site reporting timelines: All SAEs and device deficiencies must be reported to Edwards immediately, but no later than 3 calendar days after site study personnel's awareness of the event. Other AEs must be reported to Edwards as soon as possible.

In the event that the EDC system is not in service, a paper copy of the AE Case Report Form (CRF) must be faxed or emailed to Sponsor THV Medical Safety at (949) 809-2933 or emailed to THV_Safety@edwards.com. At the time of initial notification, the following minimal information must be provided:

- Study site
- Patient ID
- Adverse event description
- Causal relationship to device and implant procedure
- Aware date

The site must provide a copy of supporting documentation (example: admission H&P, implant procedure reports, anesthesia records, discharge summary, echocardiogram and ECG reports, laboratory results, etc.) for all SAEs and UADEs to Edwards Lifesciences (or designee). Source documentation may be requested by the Edwards Medical Safety Officer for other AEs in order to verify that events are being assessed appropriately.

Enrolling sites must provide to the Sponsor at a minimum an admission history and physical, index procedure report and discharge from index hospitalization along with relevant echocardiographic reports. This will be done irrespective of subject having any AE/SAE..

All AEs and SAEs regardless of device/procedure relationship must be reported over the 12-month period following the THV implant procedure. Reportable AEs after year 1 through year 10 or study exit include only the following events:

- All study endpoint events regardless of time of onset (e.g., stroke at 3 years)
- All AEs that are assessed or suspected to be device or implant procedure related
- All AEs that meet the criteria for serious adverse event irrespective of device or implant procedure relationship
- All AEs that result in emergency department/observation unit visit
- All AEs considered to be an Unanticipated Adverse Device Effect

The site Principal Investigator is responsible for informing the IRB/EC of SAEs, UADE and/or AEs as required. A copy of this report should be provided to the Sponsor (or designee).

9.3.1 Events that do not Require Reporting to the Sponsor

For purposes of this study, the following events will not be required to be reported as adverse events to the Sponsor (unless required by local regulations), because they are normally expected to occur in conjunction with transcatheter valve implantation or are associated with customary, standard care of patients undergoing THV implantation:

- Post-operative pain.
- Post-anesthesia emesis, nausea, or headache (within 24 hours of procedure).
- Electrolyte imbalance without clinical sequelae following procedure, even if requiring correction.
- Low grade temperature increase (≤ 101°F or 38.5°C).
- Dizziness: Imprecise term commonly used to describe various symptoms such as faintness, giddiness, imbalance, lightheadedness, unsteadiness or vertigo without signs of TIA or stroke.
- Elevated white blood count, outside the standard laboratory normal value, without signs and symptoms of infection.
- Minor, localized tenderness, swelling, induration, oozing, etc. at incision / delivery system insertion site.
- Systolic or diastolic blood pressure changes that do not require treatment or intervention.
- Thrombocytopenia: does not become an AE until treatment is administered. Suspected heparin-induced thrombocytopenia (HIT) should be reported.
- Hyperglycemia - The use of insulin in the post-operative period does not constitute hyperglycemia if during the index hospitalization. An elevated blood sugar of less than 250 mg/dl during the first 48 hours post-operative does not constitute hyperglycemia.
- Expected, non-clinically significant events such as non-significant lab variances.

9.4 Pre-existing conditions

Pre-existing medical conditions or symptoms reported prior to subject enrollment will not be recorded as an AE. In the event there is a worsening of the pre-existing medical condition or symptoms due to the device, implant procedure, or study related procedures, then an AE must be recorded.

9.5 Sponsor Assessment of AEs

All AEs will be reviewed by a Medical Safety Officer. Each AE will be assessed for the following:

- Relationship to the study device and/or implant procedure
- Anticipated/Unanticipated (based on the list of potential risks provided in Section 10.2 of this protocol and the applicable IFU)
- Seriousness (based on SAE criteria)

10 RISKS AND BENEFIT ANALYSIS

There are potential risks associated with transcatheter valve replacement. There are risks related to the overall procedures (complications associated with standard cardiac catheterization, local and/or general anesthesia) as well as additional possible risks uniquely associated with the use of the study valve and its delivery systems.

10.1 Potential Benefits

There are no guaranteed benefits from participation in this study. Information gained from this study may be of benefit to other people with the same medical condition in the future. The long-term results of using the SAPIEN 3 THV are not known at the present time. Alternative treatments include surgical MVR and medical management.

Implantation of the transcatheter heart valve may result in improved valvular function, acute alleviation of symptoms related to mitral stenosis, and improved quality of life in patients with a failing surgical bioprosthetic valve.

10.2 Potential Risks

There are potential risks associated with THV implantation. There are risks related to the overall procedures (complications associated with standard cardiac catheterization, balloon valvuloplasty, local and/or general anesthesia) as well as additional possible risks uniquely associated with the use of the study valve and its delivery systems.

Potential risks associated with anesthesia and interventional procedures include but are not limited to:

- Abnormal lab values (including electrolyte imbalance)
- Allergic reaction to anesthesia, contrast media, or device materials
- Anemia
- Angina
- Arrhythmia
- AV fistula or pseudoaneurysm
- Bleeding
- Cardiovascular injury including perforation or damage of vessels, ventricle, atrium, myocardium or valvular structures that may require intervention
- Conduction system defect which may require a permanent pacemaker
- Death
- Embolization including air, calcific valve material, or thrombus
- Exercise intolerance or weakness
- Fever
- Heart failure
- Heart murmur
- Hematoma
- Hemorrhage requiring transfusion or intervention
- Hypertension or hypotension
- Infection including septicemia and endocarditis
- Inflammation
- Ischemia or nerve injury
- Myocardial infarction
- Mediastinitis
- Mediastinal bleeding
- Pain or changes at the access site
- Paralysis
- Pericardial effusion or cardiac tamponade
- Permanent disability
- Pleural effusion
- Pulmonary edema
- Renal insufficiency or renal failure
- Reoperation
- Respiratory insufficiency or respiratory failure
- Restenosis
- Retroperitoneal bleed
- Stroke/transient ischemic attack, clusters or neurological deficit
- Syncope

In addition to the risks listed above, additional potential risks specifically associated with the use of the SAPIEN 3 THV, the delivery systems, and/or accessories include, but may not be limited to, the following:

- Cardiac arrest
- Cardiac failure or low cardiac output
- Cardiogenic shock
- Device degeneration
- Device embolization
- Device explants
- Device migration or malposition requiring intervention
- Device thrombosis requiring intervention
- Emergency cardiac surgery
- Hemolysis
- Left ventricular outflow tract obstruction
- Mechanical failure of delivery system, and/or accessories
- Non-emergent reoperation
- Nonstructural dysfunction
- Paravalvular or transvalvular leak
- Structural valve deterioration (wear, fracture, calcification, leaflet tear/tearing from the stent posts, leaflet retraction, suture line disruption of components of a prosthetic valve, thickening, stenosis)
- Transvalvular flow disturbance
- Valve deployment in unintended location
- Valve regurgitation
- Valve stenosis
- Valve thrombosis

10.2.1 Risk Minimization

Product handling and implant procedure guidance are provided in the IFU and training manual, which will be used for device training to minimize risks associated with device use.

Additionally, efforts will be made to minimize risks through site/investigator selection and management. First, site and investigator selection criteria are established to ensure that the study personnel and their institutions are qualified to screen, perform and manage the study procedures as well as support the associated requirements for research. Second, the trial management structure is designed to provide disciplined oversight of the trial activities including close monitoring of site and personnel performance and also support opportunities for investigators and study personnel to share best practices through investigator meetings, ongoing education and case reviews.

The SAPIEN 3 THV represents a third generation THV for Edwards Lifesciences and was developed with the experience from the first and second generation SAPIEN THVs. The SAPIEN 3 System has undergone extensive clinical testing in the aortic position and is commercially

available for TAVR, including for use in high surgical risk patients with a failing surgical aortic or mitral bioprosthesis, in the US and countries that honor the CE mark.

11 STATISTICAL ANALYSIS

11.1 Sample Size Calculations

The sample size for the study is determined empirically.

11.2 Analysis Populations

The All Treated (AT) population will be the primary population for trial endpoint analysis and will consist of all patients for whom the index procedure is begun, whether or not the index procedure is completed. If multiple procedures are attempted for the study valve implant, the last procedure with the study valve successfully deployed will be considered the index procedure and the date of the index procedure will be used for determining all follow-up visits and related assessments. The Valve Implant (VI) population is a subset of the AT population consisting of all patients who receive and retain the intended valve during the index procedure.

11.3 Timing

- For AT analyses the index procedure date will be day 0.
- Time to event will be computed by subtracting the event date minus the index procedure date (day 0). For example, if the procedure occurs on January 1, and the patient dies on January 31, the death will be considered a 30-day death for analysis.
- The timing for all visits will be based on the index procedure date. If the patient never receives the procedure, the patient won't be included in AT population and the 30-day visit will never be due; All visits for such patients will be based on the enrollment date.
- In analysis of time-dependent variables, one year is defined as 365.25 days, and one month as 30.4375 (= 365.25/12) days.

11.4 Primary Endpoint Analysis

Non-hierarchical composite endpoint of all-cause mortality and stroke at 1-year post-procedure will be summarized using a Kaplan-Meier (KM) method. All-cause mortality and stroke will be adjudicated by the CEC.

11.5 Secondary Endpoints

Each of the four secondary endpoints with statistical inference for labeling will be compared to baseline measurements. To keep overall type I error of 0.05, a gatekeeping method39 will be applied for multiplicity adjustment. The four secondary endpoints will be evaluated in the hierarchical order shown as in Section 6. Each endpoint will be tested using a two-sided t-test at alpha = 0.05. If any of the endpoints does not achieve statistical significance at alpha = 0.05, the

lower numbered endpoints in the list will not be considered for this purpose. Descriptive summary will be provided for each endpoint regardless if the statistical test is significant or not.

The rest of the secondary endpoints will be summarized descriptively, no statistical test will be performed. For categorical variables, the descriptive statistics will include counts and percentages. For the continuous endpoints, the descriptive statistics will include mean, standard deviation, medium, and range. For time to event endpoints, descriptive statistics will include number of patients at risk, number of patients with events and KM rate.

11.6 Additional Analyses

- Baseline data will be reported by summary statistics separately.
- The various procedural variables will be reported by summary statistics.
- Visit compliance data will be presented.
- A listing of the additional imaging (TEE or 4D CT, per local site practice) data which determines the presence or absence of leaflet thrombosis will be provided.

11.7 General Statistical Methodology

11.7.1 Time Dependent Variables

Time-dependent variables will be analyzed using the Kaplan-Meier algorithm, with standard errors computed by Greenwood's formula. The number of patients-at-risk will be computed at exact time points specified, without reference to any nominal follow-up windows.

11.7.2 Continuous and Ordinal Variables

- For continuous variables, summary statistics will include means, standard deviations, medians and range.
- For ordinal variables, summary statistics will include medians and quartiles; means of quantified ordered classes will also be presented when appropriate.
- NYHA and regurgitation will be considered as ordinal variables. Group counts and percentages will be presented for these variables.

11.7.3 Categorical Variables

- For categorical variables, summary statistics will include counts and percentages.

11.7.4 Missing Data

- Missing variables will not be imputed for planned analyses, except where otherwise specified in the Statistical Analysis Plan (SAP)

11.7.5 Adverse Event Analysis

- Adverse event analysis will involve both site and CEC reporting.
  - Where events have been adjudicated by the CEC, those adjudications will be used in preference to site reports.
  - Where site events are analyzed, the MedDRA coding will also be used.
- Adverse events to be analyzed include the composites involved in the primary and secondary endpoints, as well as all individual events contained in these composites. All these events will be adjudicated by the CEC and used for analyses.
- Adverse event tables will include counts of events, patients with event, and estimated event rates at the specific time point of interest.

  Adverse event data occurring past 30 days will be presented in the first clinical study report for the PMA as counts of events and patients with event. No formal analyses will be performed for such data.

11.7.6 Periodic Analyses

Periodic analyses may be performed during the trial to the extent required by the appropriate regulatory authorities and the DSMB.

Other than the required reports mentioned above, there will be no reporting of trial outcome data prior to the 30-day analysis close date.

11.7.7 Quality of Life Questionnaires

Quality of life questionnaires will be scored according to algorithms provided by the vendor. The various summary scores produced by the algorithms will be analyzed as continuous variables.

11.7.8 General Specifications

- Whenever applicable, confidence limits will be two sided, using alpha = 0.05.
- Unless otherwise specified, the precise form of each algorithm will be the default of SAS, using the latest release installed at Edwards at the time of analysis. This will be version 9.3 or later.

- Various CRFs will contain comment fields. Data in these fields will not be analyzed, but listings will be provided for internal use on request.

12 STUDY ADMINISTRATION

12.1 General Study Organization

Edwards Lifesciences is the Study Sponsor and has the overall responsibility for the conduct of the study, including assurance that the study meets the regulatory requirements of the appropriate regulatory bodies.

Edwards Lifesciences will be responsible for obtaining IDE approval for the study, selecting investigators, ensuring that sites have IRB/EC approval prior to investigational device shipment, and conducting clinical site monitoring to ensure that patients are being properly consented and the study is being conducted according to the protocol.

As appropriate, Edwards Lifesciences will submit changes in the Investigational Plan to the FDA and Investigators to obtain IRB/EC re-approval.

Edwards Lifesciences will maintain copies of correspondence, data, shipment of devices, adverse device effects and other records related to the clinical trial as appropriate.

Edwards Lifesciences will submit all reports required by the FDA as identified in 21 Code of Federal Regulations (CFR) 812.150(B). This includes UADEs, withdrawal of IRB/EC approval, current investigators list, annual progress reports, recall information, final reports and protocol violations.

12.2 Data Safety Monitoring Board (DSMB)

A Data Safety Monitoring Board (DSMB) will monitor all AEs and SAEs to provide safety oversight. DSMB members will not be involved in the study and have no conflict of interest. At least one member will be a cardiothoracic surgeon with specific expertise in mitral stenosis. DSMB activities, including stopping rules for early termination, will be defined in the DSMB Charter.

12.3 Clinical Event Adjudication Committee (CEC)

The Clinical Events Committee (CEC) will adjudicate endpoint events and provide assessment of SAEs and device/procedure relatedness. The CEC will include cardiologists and cardiothoracic surgeons with experience in the field of mitral stenosis who are not involved in the study and have no conflict of interest. CEC activities will be defined in the CEC Charter.

12.4 Study Procedures

12.4.1 Echocardiogram

Study patients will receive an echocardiogram at the visits specified in Section 8.0. A central imaging core lab will be established to independently review and analyze echocardiographic images. A standardized protocol for acquiring images will be developed by the core lab and be provided to the clinical sites prior to study initiation. Sites will be trained on acquiring images prior to study initiation.

12.4.2 Computed Tomography (CT)

All study patients will have a screening CT as referenced in Section 8.0. Sites will be trained on acquiring images prior to study initiation. In addition, all CTs will be independently analyzed by a CT/angiographic core lab.

12.4.3 Quality of Life Questionnaires

Investigational sites will be provided with paper QoL questionnaires (KCCQ, EQ-5D-5L, and the SF-36). Patient questionnaires will be IRB/EC approved prior to patient administration.

Investigational staff will administer patient questionnaires to study patients. Patients will be instructed to complete each questionnaire at visits specified in Section 8.0. The patient will be instructed by the investigational staff to sign and date the paper questionnaire once the questionnaire is completed. Patients will be instructed by the investigational staff not to change questionnaire answers once the questionnaire has been completed. Investigational sites should retain the completed questionnaire in the patients' source documents. Site staff will enter data collected from the completed patient questionnaire into the EDC.

The patient level summary scores will be computed by the Edwards Biostatistics group, and these scores will be used in evaluating protocol endpoints.

Quality of life will be measured through standard surveys:

- The Kansas City Cardiomyopathy Questionnaire (KCCQ) is an assessment of disability and quality of life impairment due to congestive heart failure.
- EQ-5D-5L is a standardized questionnaire for describing and valuing patients' health-related quality of life for clinical and economic appraisal.
- The SF- 36 is a generic health status instrument and rating scale that allows mapping of health status to population-level utility weights. This is an important metric for cost-effectiveness analysis.

12.4.4 Image Management

A image transfer vendor will be established to receive, maintain, and provide cardiac images (echocardiogram, fluoroscopy and CT) to the appropriate core lab for analysis.

Instructions for image upload will be provided to investigative staff prior to study initiation. Investigative staff should make every reasonable effort to upload procedural images to the image transfer vendor within 1 business day of acquisition. All other images should be uploaded within 5 business days of image acquisition. Any unscheduled imaging performed related to the safety or performance of the device should also be uploaded.

12.4.5 Histopathology

Histopathology will be performed on all explanted valves. Explants will be prepared, preserved and shipped to the Histopathology Core Lab per instructions provided by Edwards.

12.5 Training

To ensure proper device usage, uniform data collection, and protocol compliance, training is required for relevant study site personnel in accordance to roles outlined in the Delegation of Authority (DoA).

At the beginning of the study, Edwards Lifesciences will provide training to site personnel. Training will include review of the instructions for use of the device, study protocol, case review process, identification of eligible patients, instructions on in-hospital data collection, standardized data collection for core laboratory analysis, methods for soliciting data from alternative sources, and regulatory requirements.

Documentation of site personnel qualification and training should be maintained in the site's clinical trial files and copies collected and forwarded for the Sponsor site file.

Ongoing training may be provided in one of the following formats by the Sponsor or its designee: live training sessions, teleconference, WebEx, online, or read and review. The Sponsor reserves the right to enforce retraining for sites who have demonstrated study or implant procedure compliance issues.

12.6 Device Management

12.6.1 Study Device

All SAPIEN 3 products will be supplied by Edwards Lifesciences. Each SAPIEN 3 THV will have a unique identifier which should be recorded in the patient's medical file as well as on the implant card that is given to the patient.

12.6.2 Device Storage

All SAPIEN 3 System components provided for the study should be stored in a secure location where only study personnel can access the device for use. Only physicians identified in the Investigator's Delegation of Authority Log on file at Edwards Lifesciences may implant this device in study patients.

12.6.3 Device Accountability

The study site will maintain detailed records of the receipt and disposition of all investigational devices on the Device Accountability Log (DAL). Device disposition will be verified by the clinical monitor periodically throughout the study. The Investigator will return unused devices to Edwards along with the completed device disposition log at completion of the investigation. Use of the SAPIEN 3 THV and accessories provided for use in the study is prohibited outside of this protocol.

12.7 Data Management

Edwards Lifesciences will provide data management through a secure, password protected EDC system accessible by sites via the Internet. A unique Patient ID will be assigned for each patient enrolled in the study. All pertinent data will be entered by the study site and core lab personnel into the electronic Case Report Forms (eCRFs).

Every reasonable effort should be made to complete data entry within 5 business days of data collection. Data review by Edwards Lifesciences personnel will occur remotely as well as during on site monitoring. Data discrepancies will be queried and resolved through the EDC system.

The site Principal Investigator or designee must ensure the accuracy and completeness of the recorded data and then provide his/her electronic signature on the appropriate eCRFs. Changes to data previously submitted to the Sponsor will require a new electronic signature to acknowledge/approve the changes.

12.8 Monitoring Procedures

All clinical sites will be monitored periodically by Edwards Lifesciences or designee to ensure compliance with the protocol and the Investigator's Agreement and that all study patients have been properly consented. The monitor will ensure that the completed eCRFs match the source documents and work with the site to resolve differences through queries or formal action items.

Edwards Lifesciences will evaluate circumstances where an investigator deviates from the clinical protocol and will retain the right to remove either the investigator or the investigational site from the study.

12.9 Auditing

The study may be subject to a quality assurance audit by Edwards Lifesciences or a designee, as well as inspection by appropriate regulatory authorities. It is important that the Investigator

and relevant study personnel are available during any audits and that sufficient time is devoted to the process. In the event of an audit by regulatory authorities, the Investigator should contact Edwards Lifesciences as soon as possible.

12.10 Record Retention

All clinical sites will maintain study records for a minimum of two years after marketing for this patient population approval is obtained or after the site is notified by Edwards

Lifesciences that the study has been terminated. Record retention dates will be provided to all parties concerned by Edwards Lifesciences.

13 ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Applicable Principles and Regulations

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki (as updated in Fortaleza Brazil in 2013) and in compliance with Title 21 Code of Federal Regulations (CFR) Parts 11, 50, 54, 56, 812 and Good Clinical Practices. Specific country regulations will be fulfilled, as applicable.

13.2 Institutional Review Board/Ethics Committee

This protocol, the proposed Informed Consent Form (ICF), other written patient information and any proposed advertising material must be submitted to the IRB/EC for written approval. A copy of the written IRB/EC approval of the protocol and ICF must be received by Edwards Lifesciences before recruitment of patients into the study and shipment of investigational product.

The Investigator must submit and, where necessary, obtain approval from the IRB/EC for all subsequent protocol amendments and changes to the ICF.

The Investigator is responsible for obtaining annual IRB/EC approval and renewal throughout the duration of the study. Copies of the Investigator's reports and the IRB/EC continuance of approval must be sent to Edwards Lifesciences.

13.3 Patient Informed Consent

Edwards Lifesciences will provide a sample ICF to the Investigator to prepare for use at his/her site. The site-specific ICF must be in agreement with current GCP guidelines.

Edwards Lifesciences must approve the site-specific ICF prior to submission to the IRB/EC. The reviewing IRB/EC must approve the ICF before use at that site.

Before participating in the clinical trial, each patient must give written Informed Consent after the context of the study has been fully explained in a language that is easily understood by the patient. The subject must also be given the opportunity to ask questions and have those questions answered to his/her satisfaction.

A copy of each patient's signed and self-dated consent form must be maintained by each Investigator in a designated clinical trial administrative file. A signed copy of the consent form must be given to each subject. The consent process must be documented in the subject's medical chart.

Any modifications to the site-specific ICF must be approved by Edwards Lifesciences and the IRB/EC.

13.4 Confidentiality

All data used in the analysis and reporting of this evaluation will be without identifiable reference to the patient. Authorized personnel assigned by Edwards Lifesciences will have access to the confidential files and will have the right to inspect and copy all records pertinent to this trial. All data used in the analysis and reporting of this evaluation will be without identifiable reference to the subject.

13.5 Investigator Records

Records to be maintained by the Investigator include, but are not limited to, the following:

- Clinical trial protocol and all amendments
- Signed Clinical Trial Agreement and any amendments
- IRB/EC approval letters, including continuing reviews and all amendments/changes
- IRB/EC approved informed consent documents

The following records must be maintained for each subject enrolled in the trial:

- Signed patient informed consent
- All relevant source documentation for study visits and study-related procedures
- Supporting documentation of any adverse events

13.6 Investigator Reports

Adverse event reporting requirements are discussed in Section 9.2.

Withdrawal of IRB/EC Approval. Within 5 working days, the Principal Investigator will report to Edwards Lifesciences a withdrawal of approval by the reviewing IRB/EC of the investigator's part of an investigation.

Informed Consent. If an investigator uses a device without obtaining informed consent, the investigator shall report such use to Edwards Lifesciences and the reviewing IRB/EC within 5 working days after the use occurs.

Progress Reports. The Principal Investigator will submit progress reports on the investigation to Edwards Lifesciences and the IRB/EC at least yearly.

Final Report. Upon completion or termination of this Trial, the Principal Investigator must submit a final written report to Edwards Lifesciences and the IRB/EC as required by the regulations. The report must be submitted within 3 months of completion or termination of the trial.

13.7 Amending the Protocol

This protocol must be followed exactly. It can be altered only by written amendments made by Edwards Lifesciences. Following appropriate approval by Edwards Lifesciences, the amended protocol will be submitted to the required regulatory agencies before being distributed to all enrolling sites. Each site must obtain IRB/EC approval and complete required training (if any, and as required by DoA role).

13.8 Protocol 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. Emergency changes to protect the life of the patient do not require prior approval but must be reported to Edwards Lifesciences and the reviewing IRB/EC within 5 days of the incident.

Each deviation from the protocol must be documented with the date and reason for the deviation and reported to Edwards Lifesciences as soon as possible, and to the IRB/EC per local guidelines and government regulations.

13.9 Publication Policy

Publication or presentation of the overall clinical study results and/or site-specific results requires prior written approval of Edwards Lifesciences. If Edwards Lifesciences approves the publication or presentation of the overall clinical study results and/or site-specific results, then Institutions and Investigators will comply with the Publications and Public Disclosure section of the Clinical Trial Agreement. Edwards Lifesciences will provide statistical support for the publication process.

All corresponding publications will be in accordance with the International Committee of Medical Journal Editors Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (updated December 2015).

Results from the clinical study will be made available to the public within 24 months after the end of data collection or if the study is terminated early.

Appendix A Abbreviations

Abbreviation	Full Term
ACT	Activated Clotting Time
ADL	Activities of Daily Living
AE	Adverse Event
AF	Atrial Fibrillation
AKI	Acute Kidney Injury
ALT	Alanine Aminotransaminase
AR	Aortic Regurgitation
AS	Aortic Stenosis
ASA	Aspirin
AST	Aspartate Aminotransaminase
AT	All Treated
AV	Atrioventricular
AVR	Aortic Valve Replacement
BAV	Balloon Aortic Valvuloplasty
BMS	Bare Metal Stent
BNP	B-Type Natriuretic Peptide
CABG	Coronary Artery Bypass Grafting
CAD	Coronary Artery Disease
CBC	Complete Blood Count
CCS	Canadian Cardiovascular Society
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CHF	Congestive Heart Failure
CK-MB	Creatine Kinase MB
CT	Computed Tomography
CTA	Clinical Trial Agreement
CTA	Computed Tomography Angiography
CV	Curriculum Vitae
DAL	Device Accountability Log
DES	Drug-Eluting Stent
DoA	Delegation of Authority
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
Echo	Echocardiogram

Abbreviation	Full Term
eGFR	Estimated Glomerular Filtration Rate
EMEA	Europe, Middle East, Africa
FDA	Food and Drug Administration
GCP	Good Clinical Practice
Hgb	Hemoglobin
HIT	Heparin-induced Thrombocytopenia
HOCM	Hypertrophic Cardiomyopathy with Obstruction
H&P	History and Physical
ICD	Implantable Cardioverter Defibrillator
ICF	Informed Consent Form
ICU	Intensive Care Unit
IDE	Investigational Device Exemption
IFU	Instructions For Use
INR	International Normalized Ratio
IRB	Institutional Review Board
KCCQ	Kansas City Cardiomyopathy Questionnaire
KM	Kaplan Meier
LMW Heparin	Low Molecular Weight Heparin
LVEF	Left Ventricular Ejection Fraction
LVOT	Left Ventricular Outflow Tract
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
MMSE	Mini Mental State Examination
MR/MRI	Magnetic Resonance / Magnetic Resonance Imaging
MR	Mitral Regurgitation
mRS	Modified Rankin Scale
MS	Mitral Stenosis
MV	Mitral Valve
MVR	Mitral Valve Replacement
NIHSS	National Institutes of Health Stroke Scale
NYHA	New York Heart Association
PCI	Percutaneous Coronary Intervention
PET	Polyethylene Terephthalate
PPM	Prosthetic-Patient-Mismatch
PT	Prothrombin Time
PVL	Paravalvular Leak
qd	Once Daily
QoL	Quality of Life
RV	Right Ventricle

Abbreviation	Full Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SF	Screen Failure
STS	Society of Thoracic Surgeons
SVD	Structural Valve Deterioration
TAVR	Transcatheter Aortic Valve Replacement
TEE	Transesophageal Echocardiogram
THV	Transcatheter Heart Valve
TIA	Transient Ischemic Attack
TTE	Transthoracic Echocardiogram
UADE	Unanticipated Adverse Device Effect
UF Heparin	Unfractionated Heparin
US	United States
VARC	Valve Academic Research Consortium
VI	Valve Implant
VIV	Valve-in-Valve
WBC	White Blood Cell
5-MWT	5-Meter Walk Test
6MWT	Six Minute Walk Test

Appendix B Definitions

Term	Definition	Reference/ Justification
Access Site	Any location (arterial or venous) traversed by a guidewire, a catheter or a sheath for TMVR	VARC-1
Access site related complication	Any adverse clinical consequence possibly associated with any of the access sites used during the procedure	VARC-1
Acute kidney injury	The increase in creatinine meeting at least Stage 1 must occur within 48 hours. Staging will be based on the worse stage that occurs within 7 days of the index procedure. 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) OR • Urine output <0.5 ml/kg per hour for >6 but <12 hours Stage 2 • Increase in serum creatinine to 200-299% (2.0-2.99 × increase compared with baseline) OR • Urine output <0.5 ml/kg per hour for >12 but <24 hours 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 • Urine output <0.3 ml/kg per hour for ≥24 hours OR • Anuria for ≥12 hours Patients receiving renal replacement therapy (dialysis, hemodialysis, peritoneal dialysis, hemofiltration, transplant therapy) are considered to meet Stage 3 criteria irrespective of other criteria	VARC-2
Anemia	A condition in which the blood is deficient in red blood cells, in hemoglobin, or in total volume, without clear evidence of overt bleeding, that is actionable (e.g. requires medications, transfusion etc.)	Sponsor
Angina / Cardiac chest pain	Chest pain due to an inadequate supply of oxygen to the heart muscle	Sponsor

<table>
<tr><th>Term</th><th>Definition</th><th>Reference/ Justification</th></tr>
<tr><td>Angina, grading scale</td><td>
<table>
<tr><td>Grade</td><td>Description</td></tr>
<tr><td>Grade I</td><td>Ordinary physical activity, such as walking and climbing stairs, does not cause angina. Angina occurs with strenuous, rapid, or prolonged exertion at work or during recreation</td></tr>
<tr><td>Grade II</td><td>Slight limitation of ordinary activity. Angina occurs with walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, walking in the cold, into the wind, while under emotional stress, or during the first hours after awakening. Walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions, does not cause angina</td></tr>
<tr><td>Grade III</td><td>Marked limitation of ordinary physical activity. Angina occurs with walking one to two blocks on the level and climbing one flight of stairs in normal conditions and at a normal pace</td></tr>
<tr><td>Grade IV</td><td>Inability to carry on any physical activity without discomfort. Angina syndrome may be present at rest</td></tr>
</table>
</td><td>Canadian Cardiovascular Society</td></tr>
<tr><td>Arrhythmia / Conduction System Injury (Defect)</td><td>Arrhythmia: an irregular heart rate or abnormal rhythm resulting in symptoms or requiring medical intervention.

Conduction system defect: an impairment of the electrical pathways and specialized muscular fibers that conduct impulses through the heart (ex. bundle branch block, heart block, etc.).</td><td>Sponsor</td></tr>
<tr><td>Atrial fibrillation</td><td>Atrial fibrillation > 24 hours, requiring new drug treatment / anticoagulation OR requiring chemical or electrical cardioversion</td><td>Sponsor</td></tr>
<tr><td>Atrial Septal Defect</td><td>Clinically significant ASD as a result of the study procedure with or without significant shunting</td><td>Sponsor</td></tr>
</table>

Term	Definition	Reference/ Justification
Bleeding	Any bleeding associated with transfusion, drop in Hgb of at least 3 g/dL from the baseline, or overt sign of blood loss. For instance, the threshold to report bleeding for TF-TMVR is > 100 mL blood loss during procedure. Overt bleeding is defined as any clinically obvious source of bleeding or bleeding source identified after appropriate investigation and diagnostic testing (e.g. imaging). Any procedural blood loss should be considered an overt bleeding. If the reason for Hgb drop was other than due to the overt bleeding i.e. due to hemodilution, chronic iron deficiency anemia, this will not be considered as a bleeding event. Examples of overt bleeding include pseudoaneurysm, retroperitoneal hematoma seen on CAT scan, visible access site hematoma, gross hematuria, gross GI bleeding including melena, hematemesis and hematochezia.	Sponsor
CABG	Coronary artery bypass surgery	Sponsor
Cardiac arrest	Cardiopulmonary arrest or circulatory arrest, is a sudden stop in effective blood circulation due to the failure of the heart to contract effectively or at all	Sponsor / STS
Cardiogenic shock	Sustained (>30 min) episode of systolic BP <90 mmHg and/or cardiac index <2.2 L/min/m2 determined to be secondary to cardiac dysfunction, and/or the requirement for parenteral inotropic or vasopressor agents or mechanical support (e.g., intra-aortic balloon pump, extracorporeal circulatory support, ventricular assist device) to maintain BP and cardiac index above those specified levels	2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials
Cardiac tamponade	Evidence of a new pericardial effusion associated with hemodynamic instability evident by: 1. Echo showing pericardial fluid and signs of tamponade such as right heart compromise, or 2. Systemic hypotension due to pericardial fluid compromising cardiac function	VARC-2 / STS

Term	Definition	Reference/ Justification
Hypertrophic Cardiomyopathy	Cardiomyopathy is a term applied to a wide spectrum of cardiac diseases in which the predominant feature is poor myocardial function in the absence of any anatomic abnormalities. Idiopathic hypertrophic subaortic stenosis (IHSS) is also known as hypertrophic obstructive cardiomyopathy (HOCM), and is characterized by a primary hypertrophy of the myocardium. The obstructive forms involve different degrees of dynamic subvalvar aortic obstruction from a thickened ventricular wall and anterior motion of the mitral valve. Cardiomyopathies are into three entities: 1. Dilated, characterized by ventricular dilatation and systolic dysfunction 2. Hypertrophic, characterized by physiologically inappropriate hypertrophy of the left ventricle 3. Restrictive, characterized by diastolic dysfunction, with a presentation often identical to constrictive pericarditis.	STS Congenital Heart Surgery Database Data Specifications
Cerebrovascular disease	Cerebrovascular disease includes all disorders in which an area of the brain is temporarily or permanently affected by ischemia or bleeding and one or more of the cerebral blood vessels are involved in the pathological process It includes: • Stroke • TIA • Noninvasive or invasive arterial imaging test demonstrating >=50% stenosis of any of the major extracranial or intracranial vessels to the brain • Previous cervical or cerebral artery revascularization surgery or percutaneous intervention This does not include chronic (nonvascular) neurological diseases or other acute neurological insults such as metabolic and anoxic ischemic encephalopathy	STS

Term	Definition	Reference/ Justification
Congestive Heart Failure (CHF)	Diagnosis requires physician documentation or report of any of the following: • Unusual dyspnea on light exertion • Recurrent dyspnea occurring in the supine position • Fluid retention; or the description of rales, jugular venous distension • Pulmonary edema on physical exam, or pulmonary edema on chest x-ray presumed to be cardiac dysfunction A low ejection fraction alone, without clinical evidence of heart failure does not qualify as heart failure. An elevated BNP without other supporting documentation should not be reported as CHF	STS
Cardiopulmonary bypass (CPB)	Bypass of the heart and lungs as in open heart surgery	Sponsor
Coronary vessel compression or obstruction	Angiographic evidence of any reduction in coronary artery luminal diameter or coronary sinus diameter due to either external compression, thrombosis, embolism, dissection, or other cause	MVARC
Device	For the determination of device relationship, the study device consists of: • The Edwards SAPIEN 3 valve • The Edwards Valve Delivery System • The Edwards Expandable Sheath	Sponsor
Device (Valve) fracture	The separation of any portion of the frame into two or more parts; as may be determined by radiography, computed tomography, magnetic resonance imaging or by direct examination	Sponsor
Device malfunction	The failure of a device to meet any of its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling of the device.	FDA., 21 CFR 803.3(m)
Device (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 should not be reported as valve thrombosis	VARC-2

Term	Definition	Reference/ Justification
Endocarditis	Endocarditis must meet at least one of the following: • Fulfilment of the Duke endocarditis criteria* • Evidence of abscess, paravalvular leak, pus, or vegetation confirmed as secondary to infection by histological or bacteriological studies during a re-operation • Findings of abscess, pus, or vegetation involving a repaired or replaced valve during an autopsy	VARC-2 Durack DT, Lukes AS, Bright DK. New criteria for diagnosis of infective endocarditis utilization of specific echocardiographic findings. Duke Endocarditis Service. *Am J Med 1994;96:200-9*
EuroSCORE II	http://www.euroscore.org/calc.html	European System for Cardiac Operative Risk Evaluation
EuroSCORE, logistic	http://www.euroscore.org/calcold.html	European System for Cardiac Operative Risk Evaluation
Explant	Removal of the investigational valve implant for any reason	Sponsor
Hemolysis	Evidence of RBC destruction best explained by hemolysis (LDH >350 u/L and decreased haptoglobin based on site lab normals) and no other explanation for the findings. Microscopic evidence may be considered supportive	Sponsor
Hospitalization (repeat)	Any admission to the hospital (including an emergency department visit ≥ 24 hours) for either a diagnostic or therapeutic purpose (e.g. diuretics, inotropes, chronotropes, oral or intra-venous therapy) following discharge from the index hospitalization	Sponsor
Hypertension	Systolic pressure > 140 or a diastolic pressure > 90 mmHg	Sponsor
Hypotension	Systolic pressure < 90 or a diastolic pressure < 60 mmHg	Sponsor
Index hospitalization	The beginning of the Index Hospitalization is defined as the day the patient is admitted for valve implant procedure and continues until the patient is discharged from the hospital.	Sponsor
Infection	Known infection requiring intravenous antibiotics for other than prophylaxis, and/or extended hospitalization	Sponsor
LVOT Obstruction	Left ventricular outflow tract obstruction resulting in peak gradient increase >10 mm Hg from baseline (screening)	MVARC

Term	Definition	Reference/ Justification
Mini-mental state examination (MMSE)	A questionnaire that is used extensively in clinical and research settings to measure cognitive impairment.	Pangman, VC; Sloan, J; Guse, L. (2000). "An Examination of Psychometric Properties of the Mini-Mental State Examination and the Standardized Mini-Mental State Examination: Implications for Clinical Practice". *Applied Nursing Research* 13 (4): 209–213.
Modified Rankin Scale (mRS)	A commonly used scale for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke, as follows: 0 No symptoms at all 1 No significant disability despite symptoms; able to carry out all usual duties and activities 2 Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance 3 Moderate disability; requiring some help, but able to walk without assistance 4 Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance 5 Severe disability; bedridden, incontinent and requiring constant nursing care and attention 6 Dead	Van Swieten, J. C., et al. "Interobserver agreement for the assessment of handicap in stroke patients." Stroke 19.5 (1988): 604-607.

Term	Definition	Reference/ Justification
Mortality, all-cause	Cardiovascular mortality Any of the following criteria: • Death due to proximate cardiac cause (e.g. myocardial infarction, cardiac tamponade, worsening heart failure) • Death caused by non-coronary 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 • Sudden or unwitnessed death • Death of unknown cause Non-cardiovascular mortality Any death in which the primary cause of death is clearly related to another condition (e.g. trauma, cancer, suicide).	VARC-2
Myocardial Infarction	An acute ischemic event that is associated with documented and clinically significant myocardial necrosis Any one of the following criteria meets the diagnosis for MI: • Detection of a rise and/or fall of cardiac biomarker values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following: - Symptoms of ischemia - New or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block (LBBB) - Development of pathological Q waves in the ECG - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality • Identification of an intracoronary thrombus by angiography	STS
National Institutes of Health Stroke Scale (NIHSS)	The NIHSS can help physicians determine the severity of a stroke, predict clinical outcomes and can help guide management.	NIHSS

<table>
<tr><th>Term</th><th>Definition</th><th>Reference/ Justification</th></tr>
<tr><td>New York Heart Association Classification (NYHA)</td><td>
<table>
<tr><th>NYHA Class</th><th>Functional Capacity</th></tr>
<tr><td>I</td><td>Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.</td></tr>
<tr><td>II</td><td>Patients 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>III</td><td>Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.</td></tr>
<tr><td>IV</td><td>Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.</td></tr>
</table>
</td><td>The Criteria Committee of the New York Heart Association. (1994). Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. (9th ed.). Boston: Little, Brown & Co. pp. 253–256.</td></tr>
<tr><td>Paravalvular Leak</td><td>PVL refers to blood flowing through a channel between the structure of the implanted valve and cardiac tissue or previously implanted valve as a result of a lack of appropriate sealing</td><td>ESC / Sponsor</td></tr>
<tr><td>Peripheral vascular disease (PVD)</td><td>Includes peripheral arterial disease of upper and lower extremity, renal, mesenteric, and abdominal aortic systems, as follows:
Claudication, either with exertion or at rest
Amputation for arterial vascular insufficiency
Vascular reconstruction, bypass surgery, or percutaneous intervention to the extremities (excluding dialysis fistulas and vein stripping)
Documented abdominal aortic aneurysm with or without repair
Positive noninvasive test (e.g., ankle brachial index =< 0.9, ultrasound, magnetic resonance or computed tomography imaging of > 50% diameter stenosis in any peripheral artery, i.e., renal, subclavian, femoral, iliac) or angiographic imaging
Peripheral arterial disease excludes disease in the carotid, cerebrovascular arteries or thoracic aorta.
PVD does not include DVT.</td><td>STS</td></tr>
</table>

Term	Definition	Reference/ Justification
Pre-existing condition	A pre-existing condition is one that is present at the start of study treatment. A preexisting condition is not an adverse event unless it worsens as a result of the study treatment.	Sponsor
Prosthetic mitral valve stenosis	Prosthetic valve stenosis defined by increase in mean mitral valve gradient > 5 mmHg from post-implant 30-day echo to most recent post-implant echo AND EOA < 1.5 cm^2.	Sponsor
Prosthetic mitral valve regurgitation	Prosthetic valve regurgitation > moderate [2+] total regurgitation AND at least one grade (with 3-class scheme) or two grades (with 5-class scheme) increase in total MR from 30-days post-implant echo to post-implant echo being compared.	Sponsor
Reintervention	Any intervention that repairs, alters or replaces a previously implanted or operated valve, which occurs after the completion of the valve implant procedure and the transfer to the procedure room. These interventions include: • Balloon mitral valvuloplasty • Surgical mitral valve replacement • Valve in valve • Paravalvular leak closure	STS/AATS/Sponsor
Valve implant procedure	Placement of study device and/or additional procedures occurring in the cath lab and/or operating room which are completed prior to subject transfer to a post-procedure recovery unit (e.g. Recovery Room, ICU/CCU, etc. The valve implant procedure will be considered to have started when the first interventional access related puncture (venous or arterial) is established for TMVR. The end of the procedure will be considered once device (Edwards eSheath) removed Performance of TEE does not by itself constitute start of procedure	Sponsor

Stroke / Transient Ischemic Attack (TIA)	Diagnostic Criteria *Acute episode 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[#]:* □ Neurology or neurosurgical specialist □ Neuroimaging procedure (MR or CT scan) □ Clinical presentation alone Stroke definitions[†]: □ Non-disabling: a mRS score of less than 2 at 90 days or the last available clinical visit with evaluable data or one that does not result in an increase of at least one mRS category from an individual's pre-stroke baseline □ Disabling: a mRS score of 2 or more at 90 days or the last available clinical visit with evaluable data and an increase of at least one mRS category from an individual's pre-stroke baseline Stroke classification: □ *Hemorrhagic:* an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage. □ *Ischemic:* an acute symptomatic episode of focal cerebral, spinal, or retinal dysfunction caused by an infarction of the central nervous system tissue □ *Undetermined:* stroke with insufficient information to allow categorization as ischemic or hemorrhagic. Transient Ischemic Attack (TIA) Duration of focal or global neurological deficit <24 h, any	VARC-2

Term	Definition	Reference/ Justification
	variable neuroimaging does not demonstrate a new hemorrhage or infarct **Patients with non-focal global encephalopathy will not be reported as a stroke without unequivocal evidence based upon neuroimaging studies.* *#If a stroke is reported without evidence of confirmation of the diagnosis by one of these methods, the event may still be considered a stroke on the basis of the clinical presentation alone.* *†Modified Rankin score assessments should be made by qualified individuals according to a certification process.*	
Structural Valvular Deterioration (SVD)	Structural valve deterioration includes dysfunction or deterioration exclusive of infection or thrombosis as determined by reoperation, autopsy or clinical investigation. The term structural deterioration refers to changes intrinsic to the valve, such as wear, fracture, calcification, leaflet tear, leaflet retraction, suture line disruption of components a prosthetic valve, thickening, stenosis	Akins, Cary W., et al. "Guidelines for reporting mortality and morbidity after cardiac valve interventions." *European Journal of Cardio-Thoracic Surgery* 33.4 (2008): 523-528.
STS Adult Cardiac Surgery Risk Calculator	The Society of Thoracic Surgeons' risk models predict the risk of operative mortality and morbidity after adult cardiac surgery on the basis of patient demographic and clinical variables. http://riskcalc.sts.org/stswebriskcalc/#/	STS
Syncope	A fainting spell or loss of consciousness	STS
SYNTAX Score	An angiographic grading tool to determine the complexity of coronary artery disease. http://www.syntaxscore.com/ http://ir-nwr.ru/calculators/syntaxscore/frameset.htm	
6 Minute Walk Test	A performance-based measure of functional exercise capacity. The test measures the distance an individual is able to walk over a total of six minutes on a hard, flat surface. See more at: http://www.rheumatology.org/I-Am-A/Rheumatologist/Research/Clinician-Researchers/Six-Minute-Walk-Test-SMWT#sthash.cFCDWfkn.dpuf	ATS
THV-in-THV	An additional valve prosthesis is implanted within a previously implanted prosthesis because of suboptimal device position and/or function, during or after the valve implant procedure	VARC- 2
Transient Ischemic Attack (TIA)	See "Stroke / Transient Ischemic Attack (TIA)"	

Term	Definition	Reference/ Justification
Vascular injury	Injury that may be caused by a guidewire, vascular sheath, delivery catheter, or any balloon used for mitral valve predilatation and can include arterial or venous dissection, perforation, arteriovenous fistula, pseudoaneurysm formation, retroperitoneal hemorrhage, or incomplete arteriotomy closure. Venous injuries can include perforation, tears and thromboembolism. Cardiac vascular injury can include perforation or tearing of the major cardiac structures that require repair.	Sponsor
Valve malpositioning	Valve migration • After initial correct positioning, the device moves within its initial position but not leading to device embolization Valve embolization • The valve prosthesis moves during or after deployment such that it loses contact with its initial position Ectopic valve deployment • Permanent deployment of the valve prosthesis in a location other than intended	MVARC

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