A Prospective, Single-arm, Multicenter Study of the SAPIEN 3 Ultra System in Intermediate Risk Patients with Severe, Calcific, Aortic Stenosis Requiring Aortic Valve Replacement

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Edwards

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Clinical Protocol/Clinical Investigation Plan
Study Number: 2018-03
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Study Sponsor:
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Irvine, California 92614
USA

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PROTOCOL SYNOPSIS

Title	A Prospective, Single-arm, Multicenter Study of the SAPIEN 3 Ultra System in Intermediate Risk Patients with Severe, Calcific, Aortic Stenosis Requiring Aortic Valve Replacement
Objective	To confirm the procedural safety and performance of the SAPIEN 3 Ultra System in subjects with severe, calcific aortic stenosis who are at intermediate operative risk for standard aortic valve replacement (AVR)
Study Device	SAPIEN 3 Ultra Delivery System with the SAPIEN 3 Ultra THV (20, 23 and 26 mm) and SAPIEN 3 THV (29 mm)
Study Design	Prospective, single-arm, multicenter study
Study Population	Subjects with symptomatic, severe, calcific, aortic stenosis requiring AVR who are at intermediate operative risk and have appropriate iliofemoral anatomy for transfemoral access.
Sample Size	Up to 110 subjects who have the procedure started
Study Sites	Up to 8 actively enrolling sites
Assessment Schedule	Screening, procedure, post-procedure, discharge, 30 days, 6 months and annually through 5 years
Primary Endpoint	The primary endpoint is procedural success defined as freedom from all of the following at exit from the procedure room: • Mortality • Conversion to surgery • Moderate or severe paravalvular regurgitation
Secondary Endpoints	The following secondary endpoints will be evaluated: • Major vascular complications through discharge • Valve migration or embolization through discharge
Inclusion Criteria	Candidates must meet all of the following criteria to be included in the study: 1. Severe, calcific aortic stenosis meeting the following transthoracic echocardiogram (TTE) criteria: • Aortic valve area (AVA) ≤ 1.0 cm^2 OR AVA index ≤ 0.6 cm^2/m^2 • Jet velocity ≥ 4.0 m/s OR mean gradient ≥ 40 mmHg 2. New York Heart Association (NYHA) functional class ≥ II 3. Judged by the Heart Team 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 risk calculator) 4. The subject 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/Ethics Committee of the respective

clinical site.

Exclusion Criteria

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

1. Native aortic annulus size unsuitable for available THV sizes on 3D imaging analysis
2. Aortic valve is unicuspid, bicuspid or non-calcified
3. Pre-existing mechanical or bioprosthetic valve in any position. (Of note, mitral ring is not an exclusion)
4. Severe aortic regurgitation (> 3+)
5. Severe mitral regurgitation (> 3+) or ≥ moderate stenosis
6. Ventricular dysfunction with left ventricular ejection fraction (LVEF) < 30%
7. Cardiac imaging (echocardiography, computed tomography and/or magnetic resonance imaging) evidence of intracardiac mass, thrombus or vegetation
8. Evidence of an acute myocardial infarction ≤ 30 days before the valve implant procedure
9. Subjects with planned concomitant ablation for atrial fibrillation
10. Hypertrophic cardiomyopathy with obstruction (HOCM)
11. Coronary anatomy that increases the risk of coronary artery obstruction post-TAVR
12. Complex coronary artery disease (CAD):
    a. Unprotected left main coronary artery
    b. SYNTAX score > 32 (in the absence of prior revascularization)
    c. Heart Team assessment that optimal revascularization cannot be performed
13. Iliofemoral vessel characteristics that would preclude safe placement of the introducer sheath
14. Significant abdominal or thoracic aortic disease that would preclude safe passage of the delivery system
15. Active bacterial endocarditis within 180 days of the valve implant procedure
16. Stroke or transient ischemic attack within 90 days of the valve implant procedure
17. Symptomatic carotid or vertebral artery disease or successful treatment of carotid stenosis within 30 days of the valve implant procedure
18. Severe lung disease (Forced Ejection Volume 1 (FEV1) < 50% predicted) or currently on home oxygen
19. Severe pulmonary hypertension (e.g., pulmonary artery systolic pressure ≥ 2/3 systemic pressure)

20. Hemodynamic or respiratory instability requiring inotropic support, mechanical ventilation or mechanical heart assistance within 30 days of the valve implant procedure
21. History of cirrhosis or any active liver disease
22. Renal insufficiency (estimated glomerular filtration rate (eGFR) < 30 mL/min per the Cockcroft-Gault formula) and/or renal replacement therapy at the time of screening
23. Leukopenia (WBC < 3000 cell/mL), anemia (Hgb < 9 g/dL), thrombocytopenia (Plt < 50,000 cell/mL), history of bleeding diathesis or coagulopathy or hypercoagulable states
24. Inability to tolerate or condition precluding treatment with antithrombotic therapy during or after the valve implant procedure
25. Absolute contraindications or allergy to iodinated contrast that cannot be adequately treated with pre-medication
26. Significant frailty as determined by the Heart Team (after objective assessment of frailty parameters)
27. Subject refuses blood products
28. Body mass index > 50 kg/m^2
29. Estimated life expectancy < 24 months
30. Positive urine or serum pregnancy test in female subjects of childbearing potential
31. Currently participating in an investigational drug or another device study. Note: Trials requiring extended follow-up for products that were investigational, but have since become commercially available, are not considered investigational trials. Observational studies are not considered exclusionary.

Statistical Methods

The success criterion for this study is procedural success of at least 90%. The primary statistical analysis for this study is to estimate the procedure success rate. With sample size of at least 55 subjects, if the observed rate is at least 90%, the lower bound of the observed 95% CI (calculated from binomial distribution) will be at least 80%. Descriptive summary statistics will be provided.

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INVESTIGATOR SIGNATURE PAGE

Protocol Title: A Prospective, Single-arm, Multicenter Study of the SAPIEN 3 Ultra System in Intermediate Risk Patients with Severe, Calcific, Aortic Stenosis Requiring Aortic Valve Replacement

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.

_____
Study Site Name

_____
Site Principal Investigator Name (print)

_____ _____
Site Principal Investigator Signature Date

1 INTRODUCTION

1.1 Aortic Stenosis

Aortic stenosis (AS) is one of the most common valvular diseases in developed countries, affecting ~5% of adults above the age of 65, and its prevalence is projected to increase over the next decade with an aging population (1, 2). AS is a progressive, debilitating and life-threatening disease if left untreated. The pathology involves progressive calcification of the leaflets that results in stenosis which limits valve opening. The consequences of valve obstruction include increased afterload, left ventricular hypertrophy, and a decrease in systemic and coronary blood flow. Typically, patients with AS are free from cardiovascular symptoms (e.g. angina, syncope, and/or heart failure) until late in the course of the disease. However, once symptoms manifest, the prognosis is poor without intervention. Survival analyses have demonstrated that the interval from onset of symptoms to time of death is approximately two years in patients with heart failure, three years in those with syncope, and five years in those with angina (3).

1.2 Treatment of AS

Relief of aortic valve obstruction typically results in an improvement of symptoms, hemodynamic parameters, and global left ventricle systolic function, as well as reversal of left ventricular hypertrophy (4, 5). Treatment options for patients with severe, symptomatic AS include medical management, percutaneous balloon aortic valvuloplasty (BAV) or aortic valve replacement (AVR).

AVR is considered the gold standard for treatment of patients with severe, symptomatic AS (6). AVR may be performed surgically or percutaneously. Outcomes after surgical AVR (SAVR) are excellent in patients who do not have a high procedural risk, resulting in an improvement in symptoms, and in most patients, an improvement in exercise tolerance (7-11).

Transcatheter aortic valve replacement (TAVR) was originally developed as an alternative to SAVR in patients who were at high risk for surgical mortality or who were not suitable for surgical intervention, with the first successful TAVR procedure performed by Cribier and colleagues in 2002 (12).

The Placement of AoRtic TranNscathetER valve (PARTNER) study, Cohort B compared standard medical therapy (including BAV) to TAVR in patients with severe AS who were not candidates for surgical intervention. Mortality rates at 1 year were significantly lower in the TAVR cohort compared to those who underwent medical therapy (30.7% vs. 50.7%, $p<0.001$) (13). At 5-years, 71.8% of TAVR patients had died compared to 93.6% of patients treated medically ($p<0.0001$) (14).

Numerous studies have since been performed comparing TAVR to SAVR. Studies comparing the two treatments in patients at high surgical risk have demonstrated the superiority of outcomes with TAVR compared to SAVR (15-17)

In the PARTNER II study evaluating outcomes of TAVR with SAPIEN XT vs SAVR in intermediate risk patents, there was no difference between TAVR and SAVR for the primary endpoint of all-

cause death or disabling stroke at 2 years (Hazard Ratio: 0.89; 95% Confidence Interval (CI): 0.73 to 1.09; p=0.25). All-cause mortality occurred in 16.7% of those randomized to TAVR with SAPIEN XT, compared with 18.0% of those treated with SAVR. Disabling stroke occurred in 6.2% of patients treated with TAVR and 6.3% of patients treated with SAVR (18). In a propensity score-matched comparison of the SAPIEN 3 TAVR patients and PARTNER II Cohort A SAVR patients, TAVR demonstrator noninferiority and superiority to SAVR (propensity score pooled weighted proportion difference: –9.2%; 95% CI: –13.0 to –5.4; p<0.0001). At 1 year, the rate of all-cause death was 7.4%, disabling stroke occurred in 2%, reintervention was required in 1%, and moderate or severe paravalvular leak (PVL) was seen in 2% (19).

As a result of these and other findings, the American College of Cardiology (ACC)/American Heart Association (AHA) guideline committees have provided TAVR with a Class I and IIa recommendation for patients with severe AS with high/prohibitive and intermediate surgical risk, respectively (20). And according to the 2017 European Society of Cardiology (ESC)/ European Association for Cardio-Thoracic Surgery (EACTS) guidelines on valvular heart diseases, TAVR is favored over SAVR in elderly patients with suitable transfemoral access and elevated surgical risk (21).

This study will evaluate the SAPIEN 3 Ultra System. The SAPIEN 3 Ultra THV design differs from the SAPIEN 3 design only with respect to the weave of the outer skirt and attachment of the skirt to the frame. The SAPIEN 3 Ultra Delivery System allows the THV to be crimped directly onto the deployment balloon eliminating the need for valve alignment and reducing the number of procedural steps.

2 STUDY OBJECTIVE

The objective of this study is to confirm the procedural safety and performance of the SAPIEN 3 Ultra System in subjects with severe, calcific AS who are at intermediate operative risk for standard AVR.

2.1 Intended Use

The Edwards SAPIEN 3 Ultra valve and the Edwards SAPIEN 3 with the Edwards SAPIEN 3 Ultra delivery system and accessories are indicated for use in patients with severe, symptomatic, calcific aortic valve stenosis who are judged by a Heart Team, to be at intermediate or greater risk for open surgical therapy (i.e., predicted risk of surgical mortality ≥ 3% at 30 days, based on the Society of Thoracic Surgeons (STS) risk score and other clinical comorbidities unmeasured by the STS risk calculator).

3 STUDY DESIGN

This is a prospective, single-arm, multicenter study. Up to 110 subjects will undergo the procedure at up to 8 participating centers. Subject follow-up will occur at 30 days, 6 months and annually through five years.

4 STUDY DEVICES

The following devices and accessories will be used per the Instructions for Use (IFU) and after sufficient training has been provided by Edwards.

4.1 Edwards SAPIEN 3 Ultra THV

The Edwards SAPIEN 3 Ultra THV is comprised of a balloon-expandable, radiopaque, cobalt-chromium frame, trileaflet bovine pericardial tissue valve, and polyethylene terephthalate (PET) inner and outer fabric skirts. The leaflets are treated according to the Carpentier-Edwards ThermaFix process. See **Table 1** for THV sizing recommendations.

4.2 Edwards SAPIEN 3 THV

The Edwards SAPIEN 3 THV is comprised of a balloon-expandable, radiopaque, cobalt-chromium frame, trileaflet bovine pericardial tissue valve, and PET inner and outer fabric skirts. The leaflets are treated according to the Carpentier-Edwards ThermaFix process. See **Table 1** for THV sizing recommendations.

The THV is intended to be implanted in a native annulus size range associated with the three-dimensional area of the aortic annulus measured at the basal ring during systole.

Table 1: THV Sizing Dimensions

Native Valve Annulus Size (TEE)*	Native Valve Annulus Size (CT)		
	Area	Area Derived Diameter	THV Size
16 – 19 mm	273 – 345 mm^2	18.6 – 21.0 mm	20 mm
18 – 22 mm	338 – 430 mm^2	20.7 – 23.4 mm	23 mm
21 – 25 mm	430 – 546 mm^2	23.4 – 26.4 mm	26 mm
24 – 28 mm	540 – 683 mm^2	26.2 – 29.5 mm	29 mm

*Due to limitations in two-dimensional images, 2-D TEE imaging should be supplemented with 3-D area measurements.

THV size recommendations are based on native valve annulus size, as measured by transesophageal echocardiography (TEE) or computed tomography (CT). Patient anatomical factors and multiple imaging modalities should be considered during THV size selection. Note: Risks associated with undersizing and oversizing should be considered to minimize the risk of paravalvular leak, migration and/or annular rupture.

4.3 Edwards SAPIEN 3 Ultra Delivery System

The Edwards SAPIEN 3 Ultra delivery system which is used for delivery of the Edwards SAPIEN 3 Ultra THV and the Edwards SAPIEN 3 THV consists of a Flex Catheter to aid in tracking, and THV positioning. The delivery system includes a tapered tip to facilitate crossing of the native valve. The handle contains a Flex Wheel to control flexing of the Flex Catheter, and the Fine Adjustment Wheel to facilitate THV positioning within the native annulus. A stylet is included within the guidewire lumen of the delivery system. A radiopaque Positioning Marker in the balloon is provided to assist with THV positioning.

The Qualcrimp crimping accessory (packaged with the Edwards SAPIEN 3 Ultra delivery system) is used during THV crimping.

The loader (packaged with the Edwards SAPIEN 3 Ultra delivery system) is used to aid insertion of the delivery system into the sheath.

4.4 Edwards Axela Sheath

The Edwards Axela sheath is intended for introduction and removal of devices used with the Edwards SAPIEN 3 Ultra THV System.

The Edwards Axela Sheath contains:

a) An expandable sheath with hydrophilic coating that provides access into the target vessel while maintaining hemostasis and temporarily enlarges its diameter to allow for passage of a device.

b) Two dilators with hydrophilic coating that can either be used to dilate the vessel to accommodate the Edwards Axela sheath and/or facilitate entry and trackability of the sheath into the vessel.

4.5 Edwards eSheath Introducer Set

The Edwards eSheath Introducer Set contains:

a) An expandable sheath (eSheath) that provides access into the target vessel while maintaining hemostasis and temporarily enlarges its diameter to allow for passage of a device.

b) Two dilators with hydrophilic coating that can either be used to dilate the vessel to accommodate the eSheath and/or facilitate entry and trackability of the eSheath into the vessel.

The eSheath has been approved for use and is commercially available with the SAPIEN 3 THV.

4.6 Edwards Crimper and Crimp Stopper

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

4.7 Edwards Transfemoral Balloon Catheter, 25 mm

The Edwards Transfemoral Balloon Catheter, 25 mm size, consists of a shaft and balloon with two radiopaque marker bands that indicate the working length of the balloon. The proximal end of the device has a “Y-connector” with a balloon inflation port labeled as “BALLOON” and a guidewire lumen port labeled as “WIRE”.

5 STUDY ENDPOINTS

5.1 Primary Endpoint

The primary endpoint is procedural success defined as freedom from all of the following at exit from the procedure room:

- Mortality
- Conversion to surgery
- Moderate or severe paravalvular regurgitation

5.2 Secondary Endpoints

The following secondary endpoints will be evaluated:

- Major vascular complications through discharge
- Valve migration or embolization through discharge

6 STUDY POPULATION

The study population will be comprised of subjects with symptomatic, severe, calcific AS requiring AVR who are at intermediate operative risk and have appropriate iliofemoral anatomy for transfemoral access.

6.1 Inclusion Criteria

Candidates must meet all of the following criteria to be included in the study:

1. Severe, calcific AS meeting the following transthoracic echocardiogram (TTE) criteria:
   - Aortic Valve Area (AVA) ≤ 1.0 cm^2 OR AVA index ≤ 0.6 cm^2/m^2
   - Jet velocity ≥ 4.0 m/s OR mean gradient ≥ 40 mmHg
2. New York Heart Association (NYHA) functional class ≥ II
3. Judged by the Heart Team 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 STS risk score and other clinical co-morbidities unmeasured by the risk calculator)
4. The subject 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.

6.2 Exclusion Criteria

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

1. Native aortic annulus size unsuitable for available THV sizes based on 3D imaging analysis
2. Aortic valve is unicuspid, bicuspid or non-calcified
3. Pre-existing mechanical or bioprosthetic valve in any position. (Of note, mitral ring is not an exclusion)
4. Severe aortic regurgitation (> 3+)
5. Severe mitral regurgitation (> 3+) or ≥ moderate stenosis
6. Ventricular dysfunction with left ventricular ejection fraction (LVEF) < 30%
7. Cardiac imaging (echocardiography, CT and/or magnetic resonance imaging (MRI)) evidence of intracardiac mass, thrombus or vegetation
8. Evidence of an acute myocardial infarction (MI) ≤ 30 days before the valve implant procedure
9. Subjects with planned concomitant ablation for atrial fibrillation
10. Hypertrophic cardiomyopathy with obstruction (HOCM)
11. Coronary anatomy that increases the risk of coronary artery obstruction post-TAVR
12. Complex coronary artery disease (CAD):
    a. Unprotected left main coronary artery
    b. SYNTAX score > 32 (in the absence of prior revascularization)
    c. Heart Team assessment that optimal revascularization cannot be performed
13. Iliofemoral vessel characteristics that would preclude safe placement of the introducer sheath
14. Significant abdominal or thoracic aortic disease that would preclude safe passage of the delivery system
15. Active bacterial endocarditis within 180 days of the valve implant procedure
16. Stroke or transient ischemic attack (TIA) within 90 days of the valve implant procedure
17. Symptomatic carotid or vertebral artery disease or successful treatment of carotid stenosis within 30 days of the valve implant procedure
18. Severe lung disease (Forced Ejection Volume 1 (FEV1) < 50% predicted) or currently on home oxygen
19. Severe pulmonary hypertension (e.g., pulmonary artery systolic pressure ≥ 2/3 systemic pressure)
20. Hemodynamic or respiratory instability requiring inotropic support, mechanical ventilation or

mechanical heart assistance within 30 days of the valve implant procedure

21. History of cirrhosis or any active liver disease
22. Renal insufficiency (estimated glomerular filtration rate (eGFR) < 30 mL/min per the Cockcroft-Gault formula) and/or renal replacement therapy at the time of screening
23. Leukopenia (WBC < 3000 cell/mL), anemia (Hgb < 9 g/dL), thrombocytopenia (Plt < 50,000 cell/mL), history of bleeding diathesis or coagulopathy or hypercoagulable states
24. Inability to tolerate or condition precluding treatment with antithrombotic therapy during or after the valve implant procedure
25. Absolute contraindications or allergy to iodinated contrast that cannot be adequately treated with pre-medication
26. Significant frailty as determined by the Heart Team (after objective assessment of frailty parameters)
27. Subject refuses blood products
28. Body mass index (BMI) > 50 kg/m^2
29. Estimated life expectancy < 24 months
30. Positive urine or serum pregnancy test in female subjects of childbearing potential
31. Currently participating in an investigational drug or another device study. Note: Trials requiring extended follow-up for products that were investigational, but have since become commercially available, are not considered investigational trials. Observational studies are not considered exclusionary.

7 STUDY PROCEDURES

7.1 Informed Consent

The study investigator(s) and support staff will approach subjects with symptomatic, severe calcific AS who meet general requirements 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 subjects are interested in participating in the study, the subject will sign the IRB/EC-approved informed consent form (ICF) prior to any study-specific procedures being performed. All subjects consented should be entered into the study's Electronic Data Capture (EDC) system. Subjects will be considered enrolled once the subject signs and dates the ICF.

7.2 Screening

The screening assessments will be completed within 30 days prior to the valve implant procedure, unless otherwise noted. Screening assessments will include the following:

Systems:

- Medical History

- Physical Assessment (height, weight, blood pressure and heart rate only)
- Medications: Antithrombotics (anticoagulants, antiplatelets, thrombolytics) only

Risk:

- STS Risk Score
- EuroSCORE II

Cardiopulmonary:

- NYHA Functional Class
- 12-lead Electrocardiogram (ECG)
- Transthoracic Echocardiogram (TTE) – Qualifying TTE must be performed within 90 days prior to the valve implant procedure.
- Cardiac CT Angiography (CTA) with 3D reconstruction to determine aortic annulus area. Qualifying cardiac imaging must be performed within 1 year prior to the valve implant procedure.
- Iliofemoral CTA, including thoracic and abdominal scan with visualization of iliac and femoral arteries. Iliofemoral CTA must be performed within 1 year prior to the valve implant procedure.
- 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.
- Pulmonary Function Test – only for subjects with a history of lung disease
- SYNTAX Score – only for subjects with significant native CAD

Neurological:

- Modified Rankin Scale (mRS)

Clinical Laboratory Tests:

- White blood cell count (WBC), Hemoglobin, Platelet count
- Prothrombin Time (PT) or International Normalized Ratio (INR)
- Creatine Kinase (CK) and/or Troponins ≤ 72 hours before the valve implant procedure
- Creatinine (including calculation of eGFR per the Cockcroft-Gault formula)
- Albumin (as part of Frailty Index), total bilirubin
- Aspartame Aminotransferase (AST), Alanine Aminotransferase (ALT) – only for subjects with chronic liver disease
- Pregnancy test (urine or serum) – only for female subjects of childbearing potential

Functional:

- Frailty Index (5 Meter Walk Test, grip strength, Activities of Daily Living and serum Albumin)

7.2.1 Case Review

Before a case is submitted for review, study site personnel will screen the subject for general enrollment criteria and ensure that the subject has been entered into the EDC System. It is required that at least one site surgeon Investigator personally examine the subject to determine operative risk. Once fully screened and deemed an appropriate candidate, the site will submit the case for consideration by the Case Review Board. If the case is approved, the subject may be scheduled for the valve implant procedure. If the case is not approved, the subject's status will be terminated.

Edwards will maintain a record of the case presentation and case approval notes.

7.3 Procedure

The study devices will be used per the most current IFU for device sizing, preparation and recommended implant procedure. Only physicians appropriately trained to the use of the device and identified on the Delegation of Authority (DoA) log on file with Edwards may perform the implant procedure in study subjects.

The valve implant procedure will be considered to have started when the first interventional access-related puncture (arterial) is established. It is strongly encouraged that the procedure be performed within 14 days of Case Review Board approval.

Procedure assessments will include the following:

Systems:

- Medications: Antithrombotics only
- Adverse Events

Cardiopulmonary:

- Aortogram to assess valve placement
- Assessment of PVL by either:
  - TEE, or
  - Limited TTE and Aortogram

If the procedure is aborted (prior to or after the start of the valve implant procedure), the procedure may be re-scheduled if the subject continues to meet all eligibility criteria.

7.3.1 Antithrombotic Recommendations

Table 2 outlines the recommended antithrombotic regimen.

Table 2: Recommended Antithrombotic Regimen

Pre-Valve Implant Procedure	• Aspirin (ASA) 81-100 mg QD
	• Subjects with a bare metal stent (BMS) within one month or drug-eluting stent (DES) within 12 months should be continued on Clopidogrel/prasugrel prior to their implant procedure. • Subjects in atrial fibrillation on warfarin should be bridged with low molecular weight (LMW) or unfractionated (UF) heparin prior to the implant procedure. • Subjects with persistent or paroxysmal atrial fibrillation and not on anticoagulation will not be required to have a TEE to rule out left atrial (LA) thrombus prior to implant procedure. If intra-procedural TEE during TAVR reveals thrombus, implant procedure will be aborted and delayed until subject has been on warfarin or dabigatran for 30 days. Note: thrombus must be eliminated in order to proceed with TAVR. • In subjects undergoing concomitant TAVR/Percutaneous Coronary Intervention (PCI), 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 activated clotting time (ACT) ≥ 250 sec.
Post-Valve Implant Procedure	**Category I for Stroke Risk:** No atrial fibrillation, no recent stents • ASA 81 mg QD • Clopidogrel 300 mg load within 6 hours of the implant procedure (either pre or post) • Clopidogrel 75 mg QD for at least one month post-implant procedure
	Category II for Stroke Risk: No atrial fibrillation, recent stents • ASA 81 mg QD • Clopidogrel 75 mg QD should be continued after the implant procedure without interruption for at least one month post-BMS and 12 months post-DES
	Category III for Stroke Risk: Atrial fibrillation, no recent stents • ASA 81 mg QD • Subjects should be started on warfarin or dabigatran 24 hours post-TAVR if clinically safe and this should be continued for at least one month or indefinitely, if possible. If clinically safe, subjects started on warfarin should be bridged with UF or LMW heparin until INR therapeutic. • If subjects are not a candidate for warfarin or dagibatran, Clopidogrel 75 mg QD can be considered as an alternative.
	Category IV for Stroke Risk: Atrial fibrillation, recent stents • ASA 81 mg QD • Clopidogrel 75 mg QD for at least one month post-BMS or 12 months post-DES • Subjects should be started on warfarin or dabigatran 24 hours post-TAVR if clinically safe and continued indefinitely. If clinically safe, subject's being started on warfarin should be bridged with UF or LMW heparin until INR therapeutic.

Note: Any changes to antithrombotic regimen from study visit to study visit will be noted on the electronic Case Report Form (eCRF) including reason for change.

7.3.2 Antibiotic Prophylaxis

Study subjects should be prophylactically treated to prevent endocarditis per the recommendations of the AHA (22).

7.3.3 Contrast Media

Careful management of contrast media is required. Accurate measurement of the contrast used will be captured in the subject medical records.

7.3.4 Radiation Precautions

Radiation precautions will be adhered to per institutional standards. If a radiation-induced skin injury is suspected, the Investigator must report an adverse event, and assess and treat the subject as medically necessary.

7.4 Post-procedure

The post-procedure time period is defined as the 48 hours after the subject exits the procedure room. The following will be assessed during the post-procedure time period:

Systems:

- Medications: Antithrombotics only
- Adverse Events

Cardiopulmonary:

- 12-lead ECG

Clinical Laboratory Tests:

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

7.5 Discharge

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

The following assessments will be conducted within 24 hours of the date and time of discharge.

Systems:

- Physical assessment (weight, blood pressure and heart rate only)

- Medications: Antithrombotics only
- Adverse Events

Cardiopulmonary:

- NYHA functional class
- TTE

Clinical Laboratory Tests:

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

7.6 Follow-up

The day of the procedure is considered Day 0 and will be used to schedule all subsequent visits and calculate visit windows. Six months is defined as 180 days; one year is defined as 365 days.

7.6.1 30 Days

The following assessments will be conducted at 30 days (+7 days):

Systems:

- Physical assessment (weight, blood pressure and heart rate only
- Medications: Antithrombotics only
- Adverse Events

Cardiopulmonary:

- NYHA functional class
- TTE

7.6.2 6 Months

The following assessments will be conducted by telephone or office visit at 6 months (+30 days):

Systems:

- Medications: Antithrombotics only
- Adverse Events

7.6.3 Years 1, 3 and 5

The following assessments will be conducted at years 1, 3 and 5 (+ 45 days):

Systems:

- Physical assessment (weight, blood pressure and heart rate only)
- Medications: Antithrombotics only
- Adverse Events

Cardiopulmonary:

- NYHA functional class

7.6.4 Years 2 and 4

The following assessments will be conducted by telephone or office visit at years 2 and 4 (+ 45 days):

Systems:

- Medications: Antithrombotics only
- Adverse Events

7.7 Imaging Assessments

Imaging performed during the course of the study should follow the CT Reference Document and the Echo Manual of Operations, except for the limited TTE performed post-procedure, which is only performed to assess PVL.

7.8 Neurological Assessments

Every effort should be made to have a neurologist (or neurology fellow) perform the mRS assessment. 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 them.

Following the procedure, all subjects should be assessed to determine if there is evidence of neurological impairment. 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 a protocol-specified visit, the mRS does not need to be repeated.

7.9 Subject Disposition

The following categories of subject disposition have been defined for this trial:

Enrolled: Subjects will be considered enrolled once the ICF is signed and dated.

Discontinued: Enrolled subjects will be considered discontinued when they exit the study prior to completing all required follow-up. Potential reasons include but are not limited to:

- Study Procedure Never Started: Subjects considered enrolled that do not meet pre-procedure eligibility criteria will be exited from the study.
- Procedure Started but Study Device Never Implanted: Subjects in whom the procedure was started but did not receive a study valve will be followed for 30 days or until resolution of any adverse events related to the valve implant procedure and then exited from the study.
- Study Device Explanted: Subjects who have a surgical reintervention where the study valve is explanted will be followed for 30 days post-reintervention or until resolution of any adverse events related to the procedure and then exited from the study.

Subjects that have a valvuloplasty or valve-in-valve procedure will continue to be followed for the duration of the study.

If a subject discontinues, all attempts should be made to have the subject come into the clinic for an exit visit. An exit form indicating the reason for discontinuation will be completed. Subjects who discontinue will not be replaced.

Completed: Enrolled subjects will be considered to have completed the study when all required follow-up has been performed.

Table 3 summarizes the subject assessments at each time point.

Table 3: Schedule of Assessments

	Screening	Procedure	Post-Procedure	Discharge	30 Days	6 Months [o,p]	1, 3 ,5 Years [p]	2, 4 Years [o,p]
Visit Window (days)	- 30 [a]		+ 2 [n]		+ 7	+ 30	+ 45	+ 45
Informed Consent	X							
Medical History	X							
Physical Assessment	X			X	X		X	
Medications: Antithrombotics	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X
STS Risk Score	X							
EuroSCORE II	X							
NYHA Functional Class	X			X	X		X	
12-lead ECG	X		X					
TTE	X [b]			X	X			
Cardiac CTA	X [c]							
Iliofemoral CTA	X [c]							
Assessment of CAD	X [c,d]							
Assessment of valve placement		X						
Assessment of PVL		X [m]						
Pulmonary Function Test	X [e]							
SYNTAX Score	X [f]							
mRS [g]	X							
WBC, Hgb, Platelet Count	X		X	X				
PT or INR	X		X	X				
CK and/or Troponins	X [h]							
eGFR	X							
Creatinine	X		X	X				
Albumin, Total Bilirubin	X							
AST/ALT	X [i]							
Pregnancy test	X [j]							
Frailty Index	X [k]							
Case Review	X [l]							
Valve Implant Procedure		X						

a. Screening assessments will be completed within 30 days prior to valve implant procedure, unless otherwise noted.
b. Must be performed within 90 days prior to the valve implant procedure.
c. Must be performed within 1 year prior to the valve implant procedure.
d. Assessment of severity of 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.
e. Only for subjects with a history of lung disease.
f. Only for subjects with significant native CAD.
g. Every effort should be made to have a neurologist (or neurology fellow) perform the assessment. 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 them. Following the procedure, all subjects should be assessed to determine if there is evidence of neurological impairment. 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).
h. Required ≤ 72 hours before the valve implant procedure.
i. Only required for subjects with chronic liver disease.
j. Only for female subjects of childbearing potential (urine or serum)
k. Includes activities of daily living, 5 meter walk test, grip strength and albumin.
l. 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.
m. By TEE or Limited TTE AND Aortogram
n. Post-procedure time period is defined as the 48 hours after the subject exits the procedure room.
o. Can be done by telephone or office visit.
p. Six months is defined as 180 days; one year is defined as 365 days.

8 ADVERSE EVENTS

8.1 Adverse Event Definitions

An **Adverse Event** (AE) is any untoward medical occurrence, unintended disease or injury or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the study device. For users or other persons, this definition is restricted to events related to the study device.

AEs may be volunteered by subjects, elicited or collected via observation by the Investigator or designee, or discovered by review of clinical records by Edwards Safety team or Edwards Monitoring team. Subjects will be instructed to contact the Investigator and/or study coordinator if any significant AEs occur between study visits.

A **Serious Adverse Event** (SAE) is any adverse event that:

- Led to death;
- Led to serious deterioration in the health of the subject that either resulted in:
  - a life-threatening illness or injury;
  - a permanent impairment of a body structure or a body function;
  - in-patient or prolonged hospitalization;
  - medical or surgical intervention to prevent life-threatening illness or injury or 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 subject and require immediate medical or surgical intervention to prevent one of the aforementioned outcomes.

NOTE 1: Planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health, is not considered a serious adverse event.

NOTE 2: Permanent impairment of a body structure or a body function - An AE, which results in a substantial disruption of a person‘s ability to conduct normal life functions. This does not pertain to minor events, but to serious events which result in a significant, persistent or permanent change, impairment, damage or disruption in the subject‘s body function/structure, physical activities and/or quality of life.

NOTE 3: Life-threatening – an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Adverse Device Effects (ADE) and **Serious Adverse Device Effects** (SADE) are AEs related to the use of a medical device.

NOTE 1: This includes any AE resulting from insufficiencies or inadequacies in the IFU, 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 user error or intentional abnormal use of the medical device.

Anticipated AE means an effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report. The potential AEs associated with the procedures involved and study devices are listed in the current IFU.

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 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.

8.2 Investigator Assessment of AEs

For each AE, the Investigator will determine whether the event is related to the device and/or the implant procedure, whether it was anticipated or not anticipated (based on the list of potential risks provided in the IFU) and whether the event meets the definition of an SAE or USADE.

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

1) Not related: relationship to the device or procedures can be excluded when there is no temporal relationship, the event is not a known adverse effect of similar devices or procedures, it is not clinically plausible, or the event can be attributed to another cause.
2) Unlikely: the relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
3) Possible: the relationship with the use of the device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.
4) Probable: the relationship with the use of the device seems relevant and/or the event cannot

be reasonably explained by another cause, but additional information may be obtained.

5) Causal relationship: the event is associated with the device or with procedures beyond reasonable doubt when there is a temporal relationship, the event is a known adverse effect of similar devices or procedures, it is clinically plausible, or the event cannot be attributed to another cause.

8.3 AE Reporting Requirements

All AEs will be captured from the time of enrollment until subject participation has ended (i.e. completion of study or discontinuation). See section 8.3.1 for events that are not required to be reported to Edwards.

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 in the pre-existing medical condition or symptoms due to the device or study-related procedure, then an AE must be recorded.

Death should not be recorded as an AE, but should be reflected as an outcome to another specific AE.

If known, the diagnosis for an AE should be recorded, rather than listing individual signs and symptoms.

All AEs will be reported in subject medical records, and the appropriate eCRF throughout the duration of the study, and will be followed until resolution, stabilization or study completion.

All SAEs and Device Deficiencies that might have led to a SAE should be reported to Edwards **immediately, but not later than 3 calendar days after site study personnel's awareness** of the event.

Other AEs must be reported to Edwards as soon as practical but **no later than 10 working days of awareness**.

Information must be entered into the electronic database or, when the electronic database is not available, reported directly to the Edwards Safety Officer. In the event that the EDC system is not in service, a paper copy of the AE CRF must be e-mailed to EUTHVSafety@Edwards.com according to the timelines described above.

At the time of initial AE notification, the following minimal information must be provided:

- Subject ID
- AE term/diagnosis
- AE onset date

For selected events, the site might be requested to provide to Edwards (or designee) a copy of

anonymized supporting documentation (such as hospital record, laboratory results, autopsy results).

All AEs will be reviewed by the Edwards Safety Officer. Each AE will be assessed as to its relationship to the study device and/or implant procedure, whether it was anticipated or not anticipated, and whether it qualifies as an SAE and USADE.

Depending on the local requirements or following agreement between both parties, Edwards or the Principal Investigator will be responsible for performing safety reporting to the EC according to the relevant local regulatory requirements.

Edwards will be responsible for reporting to the National Competent Authority according to national requirements and in line with MEDDEV 2.7/3 (Serious Adverse Event Reporting) and/or MEDDEV 2.12-1 (Medical Device Vigilance System), as applicable.

8.3.1 Events that do not require reporting to Edwards

For purposes of this study, the following events will not be required to be reported as AEs to Edwards, because they are normally expected to occur in conjunction with transcatheter valve implantation or are associated with customary, standard care of subjects 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).
- 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 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.
- Dizziness: imprecise term commonly used to describe various symptoms such as faintness, giddiness, imbalance, lightheadedness, unsteadiness or vertigo without signs of TIA or stroke.

Additionally, pre-planned future surgical procedures not associated with the study procedure or device do not need to be reported.

9 RISKS AND BENEFIT ANALYSIS

9.1 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 Ultra and SAPIEN 3 THVs are not known at the present time.

Implantation of the SAPIEN 3 Ultra and SAPIEN 3 THVs may result in improved valvular function, acute alleviation of symptoms related to AS, and improved quality of life in patients with intermediate operative risk of mortality.

9.2 Potential Risks

The potential risks associated with this study can be grouped into two categories. First, there are the potential risks related to the overall procedure (standard cardiac catheterization, BAV and use of anesthesia). Second, there are the additional potential risks associated with the use of the SAPIEN 3 Ultra THV and SAPIEN 3 THV Systems.

Potential risks associated with the overall procedure including access, cardiac catheterization, local and/or general anesthesia:

- Allergic reaction to antithrombotic therapy or contrast medium or anesthesia
- Anemia
- Aneurysm
- Angina
- Arrhythmias including ventricular fibrillation (VF) and ventricular tachycardia (VT)
- Arteriovenous fistula or pseudoaneurysm
- Cardiogenic shock
- Compartment syndrome
- Death
- Dissection: aortic or other vessels
- Emboli, distal (air, tissue or thrombotic emboli)
- Hematoma
- Hypertension or hypotension
- Inflammation
- Myocardial ischemia or infarction
- Pain or changes at the access site
- Perforation or rupture of cardiac structures
- Perforation or rupture of vessels
- Pericardial effusion or cardiac tamponade
- Peripheral ischemia or nerve injury
- Pulmonary edema
- Renal insufficiency or renal failure
- Respiratory insufficiency or respiratory failure
- Syncope

- Vasovagal response
- Vessel spasm
- Vessel thrombosis/occlusion
- Vessel trauma requiring surgical repair or intervention

Additional potential risks associated with the TAVR procedure, the bioprosthesis, and the use of its associated devices and accessories include:

- Allergic/immunologic reaction to the implant
- Atrial fibrillation/Atrial flutter
- Bleeding requiring transfusion or intervention
- Cardiac arrest
- Cardiac failure or low cardiac output
- Cardiogenic shock
- Conduction system injury (defect) including atrioventricular block, which may require a permanent pacemaker
- Coronary occlusion
- Dissection, rupture, trauma of the aortic annulus and surrounding structures including ascending aorta, coronary ostia and ventricular septum
- Emergency cardiac surgery
- Hemolysis
- Infection, fever, septicemia, abscess, endocarditis
- Injury to mitral valve
- Mechanical failure of delivery system, and/or accessories, including balloon rupture and tip separation
- Silent cerebral ischemia, stroke, transient ischemic attack, cognitive impairment
- Structural valve deterioration (wear, fracture, calcification, stenosis)
- Valve deployment in unintended location
- Valve explants
- Valve migration, malposition or embolization requiring intervention
- Valve regurgitation, paravalvular or transvalvular
- Valve thrombosis

9.2.1 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. All cases will be reviewed and approved prior to the procedure to confirm that the subject is an appropriate candidate for the investigational devices. Edwards representative(s) will be present during all implant procedures to provide device-related guidance.

10 STATISTICAL ANALYSIS

10.1 Analysis Populations

Enrolled subjects will consist of all subjects who sign and date the ICF.

- The As Treated (AT) population is defined to include all enrolled subjects for whom the valve implant procedure was started.
- The Valve Implant (VI) population is the subset of the AT population consisting of all subjects who receive and retain the study valve upon leaving the procedure room. If it is necessary to implant more than one study valve (valve-in-valve), the subject will still be in the VI population..

10.2 Sample Size Considerations

The success criterion for this study is procedural success of at least 90%. The primary statistical analysis for this study is to estimate the procedure success rate. With a sample size of at least 55 subjects, if the observed rate is at least 90%, the lower bound of the observed 95% CI (calculated from binomial distribution) will be at least 80%.

10.3 Statistical Analyses

Descriptive statistics will include: number of subjects and frequencies in % for categorical variables and mean and standard deviation for continuous variables. Kaplan-Meier estimates will be calculated for survival outcomes and where appropriate for adverse event outcomes.

11 STUDY ADMINISTRATION

11.1 General Study Organization

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

Edwards will be responsible for obtaining appropriate approvals prior to study commencement, selecting investigators, ensuring that sites have IRB/EC approval prior to device shipment, and conducting clinical site monitoring to ensure that subjects are being properly consented and the study is being conducted according to the protocol. Edwards will notify investigative sites of enrollment closure.

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

11.2 Case Review Board

The Case Review Board is comprised of physicians experienced with Edwards THV products for treatment of AS in the intermediate risk population. The role of the Case Review Board is to review submitted cases to determine if the subject is an appropriate candidate for the study, with

a focus on confirming subject operative risk, valve sizing, appropriate vascular access, valve morphology and any relevant clinical factors impacting enrollment eligibility.

11.3 Echocardiographic Core Lab

An independent echocardiographic core lab will review and analyze echocardiographic images. A standardized protocol for acquiring images and training will be provided to the clinical sites prior to study initiation.

11.4 Image Management

An image transfer vendor will receive, maintain and provide cardiac images (echocardiogram and CT) to the appropriate personnel for analysis.

Instructions for image upload will be provided to study site personnel prior to study initiation. Study site personnel should make every reasonable effort to upload all images to the image transfer vendor within 5 business days of image acquisition. Any unscheduled imaging performed related to the safety or performance of the device should also be uploaded.

11.5 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.

11.6 Study Site Selection

Site and investigator selection criteria will be 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.

11.7 Site Personnel Training

Training by Edwards or its designee is required for study site personnel in accordance with the roles outlined in the DoA log. Training will include review of the device IFU, study protocol, case review process, identification of eligible subjects, instructions on data collection, standardized image acquisition, methods for soliciting data from alternative sources and regulatory requirements.

Training may be provided in one of the following formats: in-person training sessions, teleconference, online via WebEx/Skype, or read and review. Retraining may be performed for sites who have demonstrated protocol or implant procedure compliance issues.

Documentation of study site personnel qualifications and training will be maintained in the site's study files with copies sent to Edwards.

11.8 Device Management

11.8.1 Investigational Device

All investigational devices will be supplied by Edwards. Unique identifiers associated with any device should be recorded in the subject's medical file as well as on the implant card that is given to the subject.

11.8.2 Device Storage

All investigational device components provided for the study should be stored in a secure location where only study personnel can access the device for use.

11.8.3 Device Accountability

The study site will maintain detailed records of the receipt and disposition of all investigational devices. Device disposition will be verified by the monitor periodically throughout the study. The Investigator will return unused devices to Edwards along with the completed device accountability log at completion of enrollment. Use of the investigational devices and accessories provided for use in this study is prohibited outside of this protocol.

11.9 Data Management

This study will use a secure, password protected EDC system accessible via the Internet. A unique Subject ID will be assigned for each subject enrolled in the study. All pertinent data will be entered by the study site and core lab personnel into eCRFs.

Every reasonable effort should be made to complete data entry within 5 business days of data collection. Data review by Edwards 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 provide his/her electronic signature on the appropriate eCRFs at regular intervals during the study, as requested by Edwards. If changes are made to data previously signed-off, a new electronic signature will be required to acknowledge/approve the changes.

11.10 Monitoring Procedures

All study sites will be monitored periodically by Edwards or designee to ensure compliance with the protocol and the Investigator's Agreement and that all study subjects have been properly consented. The monitor will ensure that the completed eCRFs match the medical records and work with the site to resolve differences through electronically-generated queries or formal action items.

11.11 Site Discontinuation

Edwards has the right to discontinue an Investigator or study site for the following reasons:

- Failure of the Investigator to enroll subjects into the study at an acceptable rate
- Failure of the Investigator to comply with pertinent regulations of appropriate regulatory authorities
- Insufficient adherence to protocol requirements
- Submission of knowingly false information from the research facility to Edwards, the monitor, or any regulatory authority.

If a study site is discontinued, subjects enrolled prior to discontinuation will continue to be followed per the protocol.

11.12 Auditing

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

11.13 Publication Policy

Publication or presentation of the overall clinical study results and/or site-specific results requires prior written approval of Edwards. If Edwards 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 will provide statistical support for the publication process.

The study results will be made public within 24 months of the end of data collection and a full report of the outcomes will be made public no later than three (3) years after the end of data collection.

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 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).

The following regulations and guidelines will be followed:

- ISO 14155: 2011 Clinical Investigation of Medical Devices for Human Subjects - Good Clinical Practice
- MDD 93/42/EEC European Medical Device Directive 93/42/EEC (MDD)

- MEDDEV 2.7/3 revision 3 Clinical Investigations: Serious Adverse Event Reporting under Directives 90/385/EEC AND 93/42/EEC
- MEDDEV 2.12-1 revision 8: Guidelines on a Medical Device Vigilance System
- General Data Protection Regulation 2016/679
- Specific country regulations will be fulfilled, as applicable

12.2 Institutional Review Board/Ethics Committee

This protocol, the proposed ICF, other written subject 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 before recruitment of subjects 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.

12.3 Informed Consent

Edwards will provide a sample ICF to the Investigator to prepare for use at his/her site. The site-specific ICF, and any subsequent modifications, must be in agreement with current regulations and guidelines and must be approved by Edwards prior to submission to the IRB/EC. The reviewing IRB/EC must approve the ICF before use at the site.

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

A copy of each subject's signed and dated consent form must be maintained by each Investigator in a designated clinical study 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; the documentation should include minimally that consent was obtained prior to participation in the research study, date consent was obtained, and confirmation that a copy of the consent was given to the subject.

12.4 Confidentiality

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

12.5 Investigator Records

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

- Clinical study 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
- All correspondence with another Investigator, IRB/EC, Edwards or monitor
- Records of receipt, use or disposition of a device

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

- Signed ICF
- All relevant source documentation for study visits and study-related procedures
- Supporting documentation of any AEs

All enrolling sites will maintain the study records for a period of two years after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application.

12.6 Protocol Amendments

The protocol can be altered only by written amendments made by Edwards. The amended protocol will be submitted to the EC and required regulatory agencies, as applicable, before being distributed to sites. Each site must obtain IRB/EC approval, complete required training (if any, and as required by DoA role), and receive written approval from Edwards before implementing the amended protocol.

12.7 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 subject do not require prior approval, but must be reported to Edwards 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 as soon as possible, and to the IRB/EC per local guidelines and government regulations.

APPENDIX A. ABBREVIATIONS

Abbreviation	Full Term
ACC	American College of Cardiology
ACT	Activated Clotting Time
ADE	Adverse Device Effect
AE	Adverse Event
AHA	American Heart Association
AKI	Acute Kidney Injury
ALT	Alanine Aminotransferase
AS	Aortic Stenosis
ASA	Aspirin
AST	Aspartate Aminotransferase
AT	As Treated
AVA	Aortic Valve Area
AVR	Aortic Valve Replacement
BAV	Balloon Aortic Valvuloplasty
BMI	Body Mass Index
BMS	Bare Metal Stent
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CI	Confidence Interval
CK	Creatine Kinase
CKMB	Creatine Kinase MB Isoenzyme
CT	Computed Tomography
DES	Drug Eluting Stent
DoA	Delegation of Authority
EACTS	European Association for Cardio-Thoracic Surgery
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
EOA	Effective Orifice Area
ESC	European Society of Cardiology
FEV1	Forced Expiratory Volume in 1 Second
Hgb	Hemoglobin
HOCM	Hypertrophic Obstructive Cardiomyopathy
ICF	Informed Consent Form
ICU	Intensive Care Unit
IFU	Instructions For Use
INR	International Normalized Ratio

Abbreviation	Full Term
IRB	Institutional Review Board
ISO	International Organization for Standardization;
LA	Left Atrial
LMW	Low Molecular Weight
LVEF	Left Ventricular Ejection Fraction
MDD	Medical Device Directive
MI	Myocardial Infarction
MR/MRI	Magnetic Resonance / Magnetic Resonance Imaging
mRS	Modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
NYHA	New York Heart Association
OPG	Objective Performance Goal
PARTNER	Placement of AoRtic TranNscathetER
PCI	Percutaneous Coronary Intervention
PET	Polyethylene Terephthalate
Plt	Platelets
PT	Prothrombin Time
PVL	Paravalvular Leak
QD	Every Day / Daily
SADE	Serious Adverse Device Effect
SAVR	Surgical Aortic Valve Replacement
SAE	Serious Adverse Event
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
USADE	Unanticipated Serious Adverse Device Effect
UF	Unfractionated Heparin
VF	Ventricular Fibrillation
VI	Valve Implant
VT	Ventricular Tachycardia
WBC	White Blood Cell

APPENDIX B. DEFINITIONS

Term	Definition	Reference/ Justification
Access Site	Any location (arterial or venous) traversed by a guidewire, a catheter or a sheath for TAVR	VARC-1 (23)
Access Site Related Complication	Any adverse clinical consequence possibly associated with any of the access sites used during the procedure Planned repair of access site entry portals are not considered access site-related complications.	VARC-1, VARC-2 (24)
Acute Kidney Injury (AKI)	AKI is defined by an abrupt decrease in kidney function • Reportable AKI is for any creatinine with an increase in serum creatinine to > 150% of baseline, OR • increase of ≥ 0.3 mg/dL compared to baseline within 48 hours of index procedure, OR • Urine output < 0.5 mL/kg per hour for > 6 but < 12 hours Patients receiving renal replacement therapy (dialysis, hemodialysis, peritoneal dialysis, hemofiltration, transplant therapy) are considered to meet Stage 3 AKI criteria. For AKI diagnosis beyond Index Procedure (or for subjects who do not get Index Procedure), the same criteria are to be used with a pre-AKI diagnosis baseline. Note: AKI stage will be determined per VARC-2 criteria.	AKIN / KDIGO / VARC-2 / Sponsor
Angina / Cardiac Chest Pain	Chest pain due to myocardial ischemia caused by an imbalance between myocardial blood supply and oxygen demand.	Sponsor
Aortic Dissection	Aortic dissection is defined as separation of the layers within the aortic wall. Tears in the intimal layer could have blood entering intima-media space resulting in the propagation of dissection (proximally or distally).	Sponsor
Aortic Stenosis, Native	Aortic stenosis is classified as “severe” when the following are present: • Jet velocity ≥ 4.0 m/s • Mean gradient ≥ 40 mmHg • Valve area ≤ 1.0 cm^2 • Valve area index ≤ 0.6 cm^2/m^2	2014 AHA/ACC
Arrhythmia / Conduction System Injury (Defect)	Arrhythmia: an increased heart rate (> 100 beats/min Tachycardia) or decreased heart rate (< 60 beats/min Bradycardia) or an irregular heart rate which could result in symptoms or require medical/surgical intervention. Conduction system defect: an impairment of Sinoatrial node, Atrioventricular node or specialized muscular fibers that conduct impulses through the heart (Internodal fibers, Bundle of His, Bundle branches, Purkinje fibers).	Sponsor

Term	Definition	Reference/ Justification
Atrial Fibrillation	Atrial fibrillation is rapid irregular heart rhythm characterized by rapid and irregular beating of atria with or without associated ventricular fibrillation and has ECG characteristics of atrial fibrillation and lasts sufficiently long to be recorded on a 12-lead ECG, or at least 30 seconds on a rhythm strip. The type of atrial fibrillation includes: • Paroxysmal atrial fibrillation: Atrial fibrillation that terminates spontaneously or with intervention within 7 days of onset. Episodes may recur with variable frequency. • Persistent atrial fibrillation: Continuous atrial fibrillation that is sustained >7 days or requires medical (rate/rhythm control) or surgical intervention (Ex: ablation, cardioversion or Maze procedure). • Permanent AF: Permanent AF is used when there has been an inability to restore and/or maintain sinus rhythm with medical and/or surgical intervention.	Sponsor (25)
Bicuspid Aortic Valve	Bicuspid aortic valve is an inheritable condition where aortic valve appears on gross examination with only two cusps as a result of fusion during development. This comprises a spectrum of deformed aortic valves presenting with two functional cusps forming a valve mechanism with less than three zones of parallel apposition between cusps. Type 1: valve with one raphe Type 2: valve with two raphes	(26)

Term	Definition	Reference/ Justification
Bleeding	Overt bleeding is defined as clinically obvious (visible bleeding and bleeding identified by imaging only). Examples of overt bleeding include: • Pseudoaneurysm • Retroperitoneal hematoma seen on CAT scan • Visible access site hematoma **Actionable Bleeding** is more bleeding than expected for clinical circumstance needing increased level of care like • hospitalization • medical/surgical intervention • transfusions Thresholds for reporting procedural bleeding for SAVR procedure is bloody chest tube output > 600 mL within any 24-hour period and for TF-TAVR >100 mL total EBL (Estimated Blood Loss) from access site. These are suggested as guidelines for Site reporting of Bleeding events and clinical judgement should be used in reporting bleeding events. **All post-procedural overt bleeding** events must be reported including hematuria, melena, hematemesis, occult gastrointestinal bleeds or drop in Hgb with overt source of bleeding detected requiring transfusions etc. 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. Note: Bleeding will be adjudicated per VARC-2 and BARC criteria.	Sponsor
CABG	Coronary artery bypass graft surgery is a procedure performed to bypass partially or completely occluded coronary arteries with veins (commonly Great/Small Saphenous veins) and/or arteries (commonly Internal thoracic/Mammary artery) harvested from elsewhere in the body, thereby improving the blood supply to the coronary circulation supplying the myocardium (heart muscle).	Sponsor/ 2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials
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
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
Cardiogenic Shock	Sustained (> 30 min) episode of systolic BP < 90 mmHg and/or cardiac index < 2.2 L/min/m^2 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
Cardiopulmonary Bypass (CPB)	CPB is a form of extracorporeal circulation that temporarily takes over the function of the heart and lungs during surgery, maintaining the circulation and oxygen content of blood in the patient's body.	Sponsor
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
Congestive Heart Failure (CHF)	Heart failure develops when the heart due to an abnormality of cardiac function (detectable or not), fails to pump blood at a rate commensurate with the requirements of the metabolizing tissues or is able to do so only with an elevated diastolic filling pressure. Diagnosis requires physician documentation or report of clinical signs and symptoms of heart failure like: • Exertional dyspnea or Dyspnea at rest • Orthopnea or Paroxysmal nocturnal dyspnea (PND) • Acute pulmonary edema • 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

Term	Definition	Reference/ Justification
Coronary Obstruction	Angiographic or echocardiographic evidence of a new, partial or complete, obstruction of a coronary artery lumen or ostium, either by the valve prosthesis itself, the native leaflets, calcifications, or dissection, occurring during or after the TAVR procedure. Mechanical coronary artery obstruction following TAVR includes: • impingement of the coronary ostia by the valve support structure in the setting of suboptimal valve positioning and/or 'small aortic root' anatomy; OR • displacement of native aortic valve leaflets towards the coronary ostia during TAVR	VARC-2/ STS/ Sponsor
Device	For the determination of device relationship, the study device consists of: • Edwards SAPIEN 3 Ultra THV • Edwards SAPIEN 3 THV • Edwards SAPIEN 3 Ultra Delivery System • Edwards Axela Sheath • Edwards eSheath Introducer Set	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 (CT), magnetic resonance imaging (MRI) 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. The intended performance of a device refers to the intended use for which the device is labeled.	FDA, 21 CFR 803.3(m)
Device (Valve) Thrombosis	Any thrombus attached to or near an implanted valve that is an incidental imaging finding (echocardiography or CT etc.) and is asymptomatic, occludes part of the blood flow path, interferes with valve function (immobility of one or more leaflets etc.), or is sufficiently large to warrant treatment. Prosthetic 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
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 (27)
EuroSCORE II	http://www.euroscore.org/calc.html	European System for Cardiac Operative Risk Evaluation
Explant	Removal of the investigational valve implant regardless of reason after the Index procedure is complete.	Sponsor

Term	Definition	Reference/ Justification
Hemolysis	The presence of a paravalvular leak on transesophageal or transthoracic echocardiography plus anemia requiring transfusion plus acute decrease in haptoglobin levels and/or increase in Serum Lactate Dehydrogenase (LDH) levels and/or standard blood examinations supporting hemolysis (Complete Blood Count, Peripheral Smear, etc.) and diagnosis of hemolysis due to prosthetic valve confirmed by a hematologist.	Sponsor
Hospitalization (repeat)	Repeat hospitalization is defined as admission to an inpatient unit or ward in the hospital or emergency department stay for ≥24 hours, for either diagnostic or therapeutic purpose. Hospitalization for the valve implant procedure (Index procedure) is not considered repeat hospitalization. Hospitalizations planned for pre-existing conditions are excluded unless there is worsening of the baseline condition.	Sponsor
Hospitalization (Valve-related or Cardiovascular)	**Prosthetic Aortic Valve-related rehospitalization** is repeat hospitalization for symptoms of prosthetic valve related decompensation due to an acute, subacute, or late valve prosthesis dysfunction such as valve stenosis, valve regurgitation, valve thrombosis, endocarditis or bleeding complications related to oral anticoagulation or antiplatelet therapy for valve-related thromboembolic event prevention. This diagnosis also requires these symptoms of valve disease not related to other diagnoses like: • documentation of anginal symptoms with no clinical evidence that angina was related to CAD or ACS • documented loss of consciousness which is not related to seizure or tachyarrhythmia **Valve Procedure-related rehospitalization** is repeat hospitalization for complications related to the index valve procedure such as bleeding and vascular complications, stroke/TIA, arrhythmias and AKI. This does not include complications indirectly related to the procedure or related to the hospitalization such as UTI, dehydration, other hospital acquired infections, etc. **Heart failure related hospitalization** is defined as repeat hospitalization for clinical symptoms, objective signs and/or diagnostic evidence of worsening heart failure and necessitating a medical intervention like administration of intravenous (Ex: IV diuretics, Vasopressors etc.) or mechanical heart failure therapies(Ex: Intra-aortic balloon pump, Left ventricular assist devices and TAVR valve reintervention etc.).	

Term	Definition	Reference/ Justification
Hypertension	Hypertension is defined as a systolic blood pressure (SBP) of 140 mmHg or more, or a diastolic blood pressure (DBP) of 90 mmHg or more, or taking antihypertensive medication.	Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)
Hypertrophic Cardiomyopathy (HOCM)	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
Hypotension	Hypotension is defined as a systolic blood pressure (SBP) lower than 90 mmHg, or mean arterial pressure (MAP) lower than 60 mmHg	Sponsor
Index Hospitalization (Index Procedure Hospitalization)	Index hospitalization is defined as the period of in-hospital stay for the prosthetic valve implant procedure. The period of Index hospitalization begins with date and time of admission for valve implant procedure and continues till the date and time the patient is discharged from the hospital where Index procedure is done.	Sponsor
Lung Disease, Severe	FEV1 < 50% predicted or currently on home oxygen	Sponsor

Term	Definition	Reference/ Justification
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	(28)
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

Term	Definition	Reference/ Justification
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: **Periprocedural MI** (≤ 72H after Index procedure) New signs or symptoms of ischemia. • Symptoms like chest pain or shortness of breath; • Ischemic signs like ECG changes indicative of new ischemia [new ST segment elevation/depression of ≥1mm in ≥2 contiguous leads or new persistent left bundle branch block (LBBB)] or • New pathological Q-waves in ≥2 contiguous leads or • Imaging evidence of a new loss of viable myocardium or new wall motion abnormality • AND Elevated cardiac biomarkers (Peak CK-MB rises post-procedure exceeding 5× the upper reference limit for CK-MB OR Peak troponin rises post-procedure exceeding 15× as the upper reference limit for troponin) • If cardiac biomarkers are increased at baseline (>99th percentile), a further increase of at least 50% post-procedure is required AND the peak value must exceed the previously stated limit. **Spontaneous MI** (Before Index Procedure or > 72 hours after the index procedure) Detection of rise and/or fall of cardiac biomarkers (preferably Troponin) with at least one value above the 99th percentile URL together with at least one of the following: • Symptoms of ischemia like chest pain or shortness of breath; • ECG changes indicative of new ischemia (new ST-segment or T-wave changes or new LBBB) or new pathologic Q-waves in ≥ 2 contiguous leads • Imaging evidence of a new loss of viable myocardium or new wall motion abnormality	STS
	MI associated with sudden, unexpected cardiac death Sudden cardiac death or cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST-segment elevation or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood **Pathologic findings of an acute myocardial infarction**	
National Institutes of Health Stroke Scale (NIHSS)	The NIHSS is a method/tool developed by the National Institutes of Health used to gauge the severity of a stroke. NIHSS is a tool to help physicians objectively determine the severity of a stroke, help predict clinical outcomes and help guide management.	NIHSS/Sponsor

<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>(29)</td></tr>
<tr><td>Paravalvular Leak (PVL)</td><td>Paravalvular or paraprosthetic leak is a complication associated with the implantation of a prosthetic heart valve whether traditional (surgical) or a transcatheter (TAVR) approach.
PVL refers to blood flowing through a channel between the structure of the implanted valve and cardiac tissue as a result of a lack of appropriate sealing</td><td>ESC</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>
<tr><td>Pulmonary Hypertension</td><td>Pulmonary hypertension (PH), defined as a mean pulmonary arterial pressure ≥ 25 mmHg at rest in the presence of Left Atrial Pressure(LAP)/Wedge pressure ≤15 mmHg and is often characterized by a progressive and sustained increase in pulmonary vascular resistance that eventually may lead to right ventricular (RV) failure</td><td>ACC/Sponsor</td></tr>
<tr><td>Pre-existing Condition</td><td>A pre-existing condition is any chronic, recurring condition identified prior to enrollment in a clinical study, whether present at enrollment or not. A preexisting condition is not an adverse event unless it worsens as a result of the study treatment.</td><td>Sponsor</td></tr>
</table>

Term	Definition	Reference/ Justification
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 aortic valvuloplasty • Surgical aortic valve replacement • Valve in valve • Paravalvular leak closure	STS/AATS
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 AND 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	VARC-2

Term	Definition	Reference/ Justification
	Confirmation of the diagnosis by at least one of the following#: • Neurology or neurosurgical specialist • Neuroimaging procedure (MR or CT scan) • Clinical presentation alone **Neurological event type classification:** **Stroke**: duration of a focal or global neurological deficit ≥24 h OR <24 h if available neuroimaging documents a new intracranial or subarachnoid hemorrhage (hemorrhagic stroke) or central nervous system infarction (ischemic stroke) OR the neurological deficit results in death. TIA**:** duration of a focal or global neurological deficit <24 h and neuroimaging does not demonstrate a new hemorrhage or infarct **Stroke etiological classification:** 1. **Hemorrhagic**: an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage. 2. **Ischemic**: an acute episode of focal cerebral, spinal, or retinal dysfunction caused by an infarction of the central nervous system tissue 3. **Undetermined**: stroke with insufficient information to allow categorization as ischemic or hemorrhagic. **Stroke severity classification:** 1. **Non-disabling**: a mRS score of <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 2. **Disabling**: a mRS score of ≥2 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	
Structural Valvular Deterioration (SVD)	Structural deterioration includes dysfunction or deterioration due to changes intrinsic to the valve, such as wear, fracture, calcification, leaflet tear, leaflet retraction, suture line disruption of components, prosthetic valve thickening, stenosis as determined by reoperation, autopsy or clinical investigation SVD excludes infection/endocarditis or thrombosis	(30)
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 subject 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 CAD. http://www.syntaxscore.com/ http://ir-nwr.ru/calculators/syntaxscore/frameset.htm	

Term	Definition	Reference/ Justification
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)”	
Valve Implant Procedure	Placement of study device and/or additional procedures occurring in the procedure 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 (arterial) is established. The end of valve implant procedure is defined as date and time of vascular closure post-eSheath removal. Performance of TEE does not by itself constitute start of procedure	Sponsor
Valve Malpositioning	**Valve migration** • After initial correct positioning, the valve prosthesis moves upward or downward, within the aortic annulus from its initial position, with or without consequences **Valve embolization** • The valve prosthesis moves during or after deployment such that it loses contact with the aortic annulus **Ectopic valve deployment** • Permanent deployment of the valve prosthesis in a location other than the aortic root	VARC-2
Vascular Injury	Injury to the vascular system that may be caused by the implanted valve or other accessories like guidewires, vascular sheaths, delivery catheters, or any balloons used for implanted valve dilatation etc. This includes arterial injuries like dissection, perforation, arteriovenous fistula, pseudoaneurysm formation, retroperitoneal hemorrhage, thromboembolism or incomplete arteriotomy closure and venous injuries like perforation, tears, or venous thrombosis including pulmonary embolism etc. and cardiac structural injuries like perforation or tearing of the major cardiac structures, pseudoaneurysm, cardiac tamponade or atrial septal defect etc.	VARC-2 / Sponsor

APPENDIX C. REFERENCES

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