EARLY TAVR

Evaluation of Transcatheter Aortic Valve Replacement Compared to SurveilLance for Patients with AsYmptomatic Severe Aortic Stenosis

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Evaluation of Transcatheter Aortic Valve Replacement Compared to SurveilLance for Patients with AsYmptomatic Severe Aortic Stenosis: EARLY TAVR trial

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PROTOCOL SYNOPSIS

Title	**E**valuation of Transcatheter **A**ortic Valve **R**eplacement Compared to Surveil**L**ance for Patients with As**Y**mptomatic Severe Aortic Stenosis: EARLY TAVR trial
Objective	To establish the safety and effectiveness of the Edwards SAPIEN 3/SAPIEN 3 Ultra Transcatheter Heart Valve (THV) compared with clinical surveillance (CS) in asymptomatic patients with severe, calcific aortic stenosis
Study Device	Edwards SAPIEN 3 THV system (20, 23, 26 and 29 mm) and Edwards SAPIEN 3 Ultra THV (20, 23 and 26 mm) with the Commander delivery system
Control	Active clinical surveillance
Study Design	Prospective, randomized, controlled, multi-center study Patients will be randomized 1:1 to receive either transcatheter aortic valve replacement (TAVR) with the Edwards SAPIEN 3/SAPIEN 3 Ultra THV or CS. Patients will be stratified by whether or not they are able to perform a treadmill stress test. In addition, patients who are screened for enrollment but have a positive stress test will be followed in a registry to collect data on subsequent treatment and mortality, as applicable.
Patient Population	Patients with asymptomatic, severe, calcific aortic stenosis and appropriate anatomy for transfemoral TAVR with the SAPIEN 3/SAPIEN 3 Ultra THV
Sample Size	900 patients will be enrolled; up to 1000 patients will be followed in the registry.
Study Sites	Up to 75 actively enrolling sites in the US will participate. Additionally, approximately 5-10 sites may be selected outside of the US.
Follow-Up Schedule	Clinical and Echocardiographic: Post Procedure (TAVR only), Discharge (TAVR only), 30 days (TAVR only), and Years 1, 2, 3 and 5. Patients randomized to the CS arm who are asymptomatic and have not undergone AVR by Year 5 will be contacted by telephone at Years 7 and 10 to assess aortic valve intervention status and survival.
Primary Endpoint	**Safety and Effectiveness:** A non-hierarchical composite endpoint of all-cause death, all stroke, and unplanned cardiovascular hospitalization The primary endpoint will be a superiority comparison using the log-rank test to compare the survival curves.
Secondary Endpoints	The following secondary endpoints will be evaluated in the Intent-to-Treat (ITT) population: • Composite of 1) alive, 2) Kansas City Cardiomyopathy Questionnaire (KCCQ) score ≥75 and 3) KCCQ decrease ≤10 points at 2 years • Integrated measure of Left Ventricular (LV) Health (LV global longitudinal

strain, LV mass index, and Left Atrial (LA) volume index) at 2 years
- Change in LV Ejection Fraction (LVEF) at 2 years
- New onset atrial fibrillation
- Death or disabling stroke

Additional Safety and Effectiveness Endpoints

The following endpoints will be analyzed in all analysis populations, as applicable. ITT and Per Protocol (PP) analyses will be based on timing post-randomization. Valve Implant (VI) analyses will be based on timing post-procedure.

1. LV global longitudinal strain at 2 years
2. LV mass index at 2 years
3. LA volume index at 2 years
4. Moderate to severe mitral regurgitation at 2 years
5. Death (all cause and cardiovascular) through 1 year and 2 years
6. Stroke (all, disabling and non-disabling) through 1 year and 2 years
7. Death or stroke through 1 year and 2 years
8. Death or disabling stroke through 1 year
9. Unplanned cardiovascular hospitalization through 1 year, 2 years, and 5 years
10. New York Heart Association (NYHA) Functional Class at 2 years
11. Six-minute walk test (6MWT) at 2 years
12. Health status as evaluated by Quality of Life questionnaires
    - KCCQ at 2 years
    - EQ-5D-5L at 2 years
    - 36-item Short Form Health Survey (SF-36) at 2 years

The following additional endpoints will be also assessed post-procedure in the VI population:

1. Death or stroke through 30 days
2. New onset atrial fibrillation through 30 days,1 year and 2 years
3. Composite of 1) alive, 2) KCCQ score ≥75 or 3) KCCQ decrease ≤10 points at 1 year and 2 years
4. NT pro-BNP at 30 days
5. Major vascular complications through 30 days
6. Bleeding complications at 30 days
7. Myocardial infarction through 30 days
8. Acute kidney injury through 30 days
9. Coronary obstruction requiring intervention through 30 days
10. New permanent pacemaker implantation resulting from new or worsened

conduction disturbances through 30 days

11. Unplanned cardiovascular hospitalization through 30 days
12. LVEF at 30 days, 1 year and 2 years
13. LV global longitudinal strain at 30 days and 1 year
14. LV mass index at 30 days and 1 year
15. LA volume index at 30 days and 1 year
16. Integrated measure of LV health at 30 days, 1 year and 2 years
17. Moderate to severe mitral regurgitation at 30 days and 1 year
18. Hemodynamic valve performance evaluation by echocardiography for aortic valve stenosis and aortic valve regurgitation (paravalvular and central) at 30 days, 1 year, 2 years and 5 years
19. Structural valve deterioration at 1 year, 2 years and 5 years
20. Length of hospital stay, ICU days and discharge location
21. NYHA Functional Class at 30 days and 1 year
22. 6MWT at 30 days and 1 year

Inclusion Criteria

Patients must meet the following inclusion criteria to be included in the trial:

1. 65 years of age or older at time of randomization
2. Severe aortic stenosis defined as:
   - Aortic valve area (AVA) ≤1.0 cm^2 or AVA index ≤0.6 cm^2/m^2 AND
   - Peak jet velocity ≥4.0 m/s or Mean gradient ≥40 mmHg
3. Patient is asymptomatic defined as:
   1) Negative treadmill stress test. To be considered asymptomatic, the patient must not demonstrate any of the following during and/or after the test:
      - Syncopal or pre-syncopal episode, including severe dizziness
      - Angina
      - Limiting dyspnea or decreased exercise tolerance, defined as inability to reach 60% of age and sex adjusted metabolic equivalents of task (METs)
      - Drop in systolic blood pressure (defined as a progressive drop of at least 20 mmHg and sustained for 1 minute or an acute drop of 40 mmHg)
      - Significant ventricular arrhythmias (≥4 consecutive ventricular premature beats)

   OR

   2) Per physician after thorough assessment of patient history if the patient is unable to perform a stress test.

4. LV ejection fraction ≥50%
5. Society of Thoracic Surgeons (STS) risk score ≤10
6. The study patient has been informed of the nature of the study, agrees to its provisions and has provided written informed consent as approved by the institutional review board of the respective clinical site.

Exclusion Criteria

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

1. Patient is symptomatic (e.g., NYHA Functional Class ≥2, history of syncopal episode, or CCS angina score >1, hospitalization for heart failure within the last 12 months).
2. Patient has any concomitant valvular, aortic, coronary artery disease requiring surgery making AVR a Class I indication.
3. Native aortic annulus size unsuitable for sizes 20, 23, 26, or 29 mm THV based on 3D imaging analysis
4. Iliofemoral vessel characteristics that would preclude safe placement of the introducer sheath.
5. Left ventricular outflow tract (LVOT) calcification that would increase the risk of annular rupture or significant paravalvular leak (PVL) post TAVR
6. Evidence of an acute myocardial infarction ≤30 days before randomization
7. Aortic valve is unicuspid, bicuspid with unfavorable features for TAVR (e.g., aneurysmal ascending aorta, i.e., >4.0 cm; severe or bulky calcification of the LVOT or raphe that would increase the risk of annular injury or significant PVL post TAVR; coronary anatomy that increases the risk of coronary artery obstruction post TAVR), or is non-calcified
8. Severe aortic regurgitation (>3+)
9. Severe mitral regurgitation (>3+) or ≥moderate mitral stenosis
10. Pre-existing mechanical or bioprosthetic valve in any position. (Of note, mitral ring is not an exclusion)
11. Symptomatic carotid or vertebral artery disease or successful treatment of carotid stenosis within 30 days of randomization
12. 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
13. Hemodynamic or respiratory instability requiring inotropic support, mechanical ventilation or mechanical heart assistance within 30 days of randomization
14. Hypertrophic cardiomyopathy with obstruction
15. Cardiac imaging (echo, CT, and/or MRI) evidence of intracardiac mass, thrombus or vegetation

16. Inability to tolerate or condition precluding treatment with anti-thrombotic therapy
17. Stroke or transient ischemic attack (TIA) within 90 days of randomization
18. Renal insufficiency (eGFR <30 ml/min per the Cockcroft-Gault formula) and/or renal replacement therapy
19. Active bacterial endocarditis within 180 days of randomization
20. Severe lung disease (FEV1 <50% predicted) or currently on home oxygen
21. Severe pulmonary hypertension (e.g., PA systolic pressure ≥2/3 systemic pressure)
22. History of cirrhosis or any active liver disease
23. Significant frailty as determined by the Heart Team (after objective assessment of frailty parameters)
24. Significant abdominal or thoracic aortic disease (such as aneurysm, severe calcification, aortic coarctation, etc.) that would preclude safe passage of the delivery system
25. Patient refuses blood products
26. BMI >50 kg/m^2
27. Estimated life expectancy <24 months
28. Absolute contraindications or allergy to iodinated contrast that cannot be adequately treated with pre-medication
29. 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.
30. Active SARS-CoV-2 infection (Coronavirus-19 [COVID-19]) or previously diagnosed with COVID-19 with sequelae that could confound endpoint assessments (as assessed by Case Review Board)

EARLY TAVR Registry Eligibility Criteria

Patients with a positive treadmill stress test should be followed in this registry if they meet the inclusion criteria 1, 2, 4, 5 and 6.

Analysis Populations

- The Intent-to-Treat (ITT) population consists of all randomized patients, analyzed in their randomized trial arms. This population is the primary population for trial arm comparisons.
- The Per Protocol (PP) population is the subset of the ITT population excluding the following patients:
    - Randomized Test patients who do not receive the TAVR procedure with a study valve.

- Randomized Control patients who withdraw from the trial without any clinical data other than baseline being available.
- Randomized Control patients who undergo surgical AVR or who receive any THV other than a study valve.

Selected trial arm comparisons will be repeated in this population.

- The Valve Implant (VI) population consists of all patients in either trial arm who receive and retain a study valve. This population will be used for echo analyses and other analyses as applicable.

Sample Size Justification

The primary endpoint will be evaluated in the ITT population and will be compared between trial arms using the log-rank test. All events post-randomization will be considered.

The cumulative event rate was determined based on preliminary aggregate data and was fitted assuming the Weibull distribution. Assuming a 10% attrition rate over 2 years and under two-sided log-rank test at alpha = 0.05, a sample size of 900 patients with equal assignment between two groups yield a study power greater than 85% if the 2-year difference between the groups is ≥ 7%. The analysis will be performed when at least 271 events are observed (projected to occur when all patients reach two years follow-up).

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INVESTIGATOR SIGNATURE PAGE

Protocol Title: Evaluation of Transcatheter Aortic Valve Replacement Compared to SurveilLance for Patients with AsYmptomatic Severe Aortic Stenosis: EARLY TAVR trial

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

_____
Investigative Site Name

_____
Site Principal Investigator Name (print)

_____ _____
Site Principal Investigator Signature Date

1 INTRODUCTION

1.1 Aortic Stenosis

Aortic stenosis (AS) affects ~5% of adults above the age of 65.[1] It is one of the most common valvular diseases in developed countries, and its prevalence is projected to increase over the next decade with an aging population.[2,3] Current American College of Cardiology (ACC)/American Heart Association (AHA) guidelines describe four stages of AS [4] as shown in **Table 1**.

The rate of hemodynamic progression of AS is variable and unpredictable. The average annual increase in aortic jet velocity has been estimated to be 0.3 m/s, and the annual decrease in aortic valve area (AVA) has been estimated at 0.1 cm^2.[5] Several predictors of rapid hemodynamic progression have been reported, including smoking, dyslipidemia, male sex, diabetes mellitus, hypertension, chronic kidney disease and coronary artery disease.[6] To what extent these factors contribute to AS progression is unknown. The aortic valve calcium load is the most powerful predictor of rapid stenosis progression.[7]

Untreated, symptomatic, severe AS is associated with a dismal prognosis,[8-10] with as many as half of patients dying within 1 or 2 years.[11-13] Aortic valve replacement (AVR), either surgical (SAVR) or transcatheter (TAVR), is the only treatment shown to improve survival.[14-18] Current guidelines recommend SAVR as a Class I indication for appropriate patients with severe symptomatic AS. TAVR is recommended with a Class I indication for severe symptomatic AS patients who are not candidates for SAVR and with a Class IIa recommendation as an alternative to SAVR in “high-risk” AS patients.[4,19]

As many as 50% of patients with severe AS report no symptoms at the time of diagnosis.[20-22] The optimal timing of intervention for these patients is uncertain and controversial.[20,22-31] Although current guidelines recommend AVR for selected patients with asymptomatic severe AS (**Table 2**),[4,19] in practice, a “watchful waiting” or active surveillance strategy with clinical and echocardiographic assessments every 6 to 12 months is adopted for the vast majority of asymptomatic patients with intervention planned once symptoms emerge or left ventricular (LV) systolic dysfunction develops.

Table 1. Stages of Valvular AS

Stage	Definition	Valve Anatomy	Valve Hemodynamics	Hemodynamic Consequences	Symptoms
A	At risk of AS	• Bicuspid aortic valve (or other congenital valve anomaly) • Aortic valve sclerosis	• Aortic V_{max} <2 m/s	• None	• None
B	Progressive AS	• Mild-to-moderate leaflet calcification of a bicuspid or trileaflet valve with some reduction in systolic motion or • Rheumatic valve changes with commissural fusion	• Mild AS: Aortic V_{max} 2.0–2.9 m/s or mean ΔP <20 mmHg • Moderate AS: Aortic V_{max} 3.0–3.9 m/s or mean ΔP 20–39 mmHg	• Early LV diastolic dysfunction may be present • Normal LVEF	• None
Stage C: Asymptomatic severe AS					
C1	Asymptomatic severe AS	• Severe leaflet calcification or congenital stenosis with severely reduced leaflet opening	• Aortic V_{max} ≥4 m/s or mean ΔP ≥40 mmHg • AVA typically is ≤1.0 cm^2 (or AVAi ≤0.6 cm^2/m^2) • Very severe AS is an aortic V_{max} ≥5 m/s or mean ΔP≥ 60 mmHg	• LV diastolic dysfunction • Mild LV hypertrophy • Normal LVEF	• None: Exercise testing is reasonable to confirm symptom status
C2	Asymptomatic severe AS with LV dysfunction	• Severe leaflet calcification or congenital stenosis with severely reduced leaflet opening	• Aortic V_{max} ≥4 m/s or mean ΔP ≥40 mmHg • AVA typically ≤1.0 cm^2 (or AVAi ≤0.6 cm^2/m^2)	• LVEF <50%	• None
D: Symptomatic severe AS					
D1	Symptomatic severe high-gradient AS	• Severe leaflet calcification or congenital stenosis with severely reduced leaflet opening	• Aortic V_{max} ≥4 m/s or mean ΔP ≥40 mmHg • AVA typically ≤1.0 cm^2 (or AVAi ≤0.6 cm^2/m^2) but may be larger with mixed AS/AR	• LV diastolic dysfunction • LV hypertrophy • Pulmonary hypertension may be present	• Exertional dyspnea or decreased exercise tolerance • Exertional angina • Exertional syncope or presyncope
D2	Symptomatic severe low-flow/low-gradient AS with reduced LVEF	• Severe leaflet calcification with severely reduced leaflet motion	• AVA ≤1.0 cm^2 with resting aortic V_{max} <4 m/s or mean ΔP <40 mmHg • Dobutamine stress echocardiography shows AVA ≤1.0 cm^2 with V_{max} ≥4 m/s at any flow rate	• LV diastolic dysfunction • LV hypertrophy • LVEF <50%	• HF • Angina • Syncope or presyncope
D3	Symptomatic severe low-gradient AS with normal LVEF or paradoxical low-flow severe AS	• Severe leaflet calcification with severely reduced leaflet motion	• AVA ≤1.0 cm^2 with aortic V_{max} <4 m/s or mean ΔP <40 mmHg • Indexed AVA ≤0.6 cm^2/m^2 and • Stroke volume index <35 mL/m^2 • Measured when patient is normotensive (systolic BP <140 mmHg)	• Increased LV relative wall thickness • Small LV chamber with low stroke volume • Restrictive diastolic filling • LVEF ≥50%	• HF • Angina • Syncope or presyncope

AR indicates aortic regurgitation; AS, aortic stenosis; AVA, aortic valve area; AVAi, aortic valve area indexed to body surface area; BP, blood pressure; HF, heart failure; LV, left ventricular; LVEF, left ventricular ejection fraction; ΔP, pressure gradient; and V_{max}, maximum aortic velocity.

This strategy has some practical challenges: 1) interpreting symptoms or the lack thereof is notoriously difficult, particularly in elderly sedentary patients; 2) with AS progression being highly variable and unpredictable, rapid deterioration may occur; 3) a standardized algorithm for active surveillance has not been defined or validated; 4) late symptom reporting may result in irreversible myocardial damage with worsened prognosis, despite AVR; 5) operative risk increases with patient age and LV dysfunction; and 6) the risk of sudden death in patients with severe AS without classic symptoms is ~1% to 1.5% per year. Given the current low periprocedural mortality rates for isolated SAVR and TAVR, earlier intervention has been increasingly advocated;[5,15-18,21,22,28-33] however, the current conservative strategy of watchful waiting in patients with asymptomatic severe AS has never been compared to early AVR in a randomized trial.

Table 2. Recommendations for the Diagnostic Evaluation, Follow-up, and Timing of Surgical Aortic Valve Replacement in Patients with Asymptomatic, Severe, High-flow, High-gradient Aortic Stenosis

	AHA/ACC [4] class (LOE)	ESC/EACTS [19] class (LOE)
Indications for surgical aortic valve replacement		
• Left ventricular ejection fraction <50%	I (B)	I (C)
• Undergoing other cardiac surgery	I (B)	I (C)
• Symptoms on exercise test clearly related to aortic stenosis	I (B)	I (C)
• Decreased exercise tolerance	IIa (B)	IIa (C)
• Exercise fall in blood pressure	IIa (B)	IIa (C)
• Very severe (aortic velocity ≥5.0 m/s [AHA/ACC]; >5.5 m/s [ESC/EACTS]) aortic stenosis and low surgical risk	IIa (B)	IIa (C)
• Rate of peak transvalvular velocity progression ≥0.3 m/s per year and low surgical risk	IIb (C)	IIa (C)
• Repeated markedly elevated natriuretic peptide and low surgical risk	—	IIb (C)
• Increase of mean pressure gradient with exercise by >20 mm Hg and low surgical risk	—	IIb (C)
• Excessive left ventricular hypertrophy in the absence of hypertension and low surgical risk	—	IIb (C)
Diagnostic evaluation		
• Transthoracic echocardiography as the initial diagnostic modality	I (B)	—
• Exercise testing	IIa (B)	—
• Exercise echocardiography	IIa (B)	—
Follow-up		
• Echocardiography every 6-12 months	I (C)	—

ACC = American College of Cardiology; AHA = American Heart Association; EACTS = European Association for Cardio-Thoracic Surgery; ESC = European Society of Cardiology. LOE = level of evidence

Of note, the level of evidence substantiating each of these recommendations is either B or C, meaning that they are on the basis of small, retrospective, observational studies or expert

consensus opinions, with no randomized clinical trial data available. The data regarding which asymptomatic, severe AS patients (stage C1) might benefit from early AVR is especially sparse. Most of the studies supporting current guideline recommendations include approximately 100 to 200 patients and originate mainly from single-center experiences.[5,32-34] In addition, the stress test criteria commonly used to qualify these patients for AVR, i.e., development of exercise-limiting symptoms at low workload or an abnormal blood pressure response (i.e., hypotension or <20 mmHg increase), are derived from studies of approximately 100 patients.[33,35-38] These studies show that patients who experience any of the above criteria are more likely over time to develop symptoms, undergo AVR, or die than patients who do not display these criteria; however, the number of deaths in these studies is low, and it is not clear whether these patients would benefit from early AVR (before they progress to symptomatic (stage D)). Similarly, although patients with peak aortic velocity ≥5 m/s or ≥5.5 m/s have an increased event rate, the events are usually development of symptoms and not sudden cardiac death while asymptomatic.[28,34,39] Whether the low rate of sudden death would be reduced with early AVR is unknown and is an important consideration given the morbidity and cost of the procedure in an asymptomatic population.

1.2 Natural Course of Asymptomatic Severe AS

Patients with asymptomatic severe AS have a better prognosis than those with symptomatic severe AS;[39] however, 5 years after receiving the diagnosis, approximately two-thirds of conservatively managed patients with asymptomatic AS will develop symptoms, and 75% will have either died or undergone AVR.[21]

In patients with asymptomatic severe AS, 1-year and 5-year survival rates have been reported to range from 67% to 97% and 38% to 83%, respectively.[22,29,32,39,40] A recent retrospective analysis of 1,517 conservatively treated patients with asymptomatic severe AS by Taniguchi et al., the largest study to date, reported 1-year and 5-year survival rates of 92.8% and 73.6%, respectively.[29] However, many patients who died did so after first developing symptoms and were not referred for AVR. The risk of dying in asymptomatic patients is directly related to the severity of AS and its rate of progression.[5,21] Patients with limiting symptoms on exercise testing are significantly more likely to develop spontaneous symptoms or die than those without exercise-limiting symptoms.[38,41] Other reported predictors of death or subsequent need for AVR include age, chronic heart failure, chronic renal insufficiency and inactivity.[5,21] Beta-blocker use and higher LVEF have been associated with better prognosis.[22] Although statin use in patients with AS has been shown to decrease the rates of ischemic cardiovascular events (mainly the need for coronary artery bypass graft), its role in preventing major clinical valve-related outcomes (such as the need for AVR) has never been demonstrated.[42]

The median time to symptom onset, AVR, or death has ranged between 1 and 4 years;[5,20-22,28,29,32-34,36-40,43-55] however, the definitions of what constitutes “symptoms” have differed across studies, and some studies reported only cardiac death and/or hospitalization, rather than death and/or symptom onset. Furthermore, some studies included patients with moderate AS (stage B) as well as more severe AS. Median time to symptom onset would likely be shorter if these studies had only included patients with severe AS. Recently, from 582 propensity-matched patients with

asymptomatic severe AS, Taniguchi et al. reported the emergence of AS-related symptoms in 46.3% of patients undergoing medical observation compared with 3.2% for patients undergoing early AVR (p <0.001) at a median follow-up of 1,361 days. Importantly, up to 19.9% in the observation group compared with 3.8% in the early AVR cohort were hospitalized for heart failure (p <0.001).[29] Also, among the 291 patients treated with the conservative approach, AVR was performed in 118 patients (41%) during follow-up, with a median interval of 780 days from diagnosis.

Hemodynamic severity of AS, the degree of aortic valve calcification, positive stress test results, and LV hypertrophy have been associated with more rapid symptom onset. [5,21,22] Other factors that influence the development of symptoms include baseline functional status and level of activity, and the presence of comorbidities.[6,32,34,48] An important drawback to basing treatment decisions on whether or not a patient reports symptoms relates to the subjective nature of "symptoms". It is difficult to decipher whether patients who do not report symptoms in everyday life and/or report no symptoms on an exercise test are truly asymptomatic. AS typically progresses slowly, and symptoms may be nonspecific. Patients may therefore relate their symptoms to poor overall stamina. They may also relate their symptoms to a concomitant medical condition. Alternatively, they may adjust their activity and/or exercise level to avoid symptoms. Finally, interpreting dyspnea as a definite cardiac symptom is often equally difficult in an aging, deconditioned and overweight population.

1.3 Exercise Testing in Asymptomatic Severe AS

AVR is a Class 1 recommendation in asymptomatic patients with severe AS if clear valve-related symptoms occurred during stress test and may be reasonable (Class IIa) for abnormal blood pressure response or poor exercise tolerance by current AHA/ACC and European Society of Cardiology (ESC)/European Association for Cardio-Thoracic Surgery (EACTS) guidelines.[4,19] The incidence of an abnormal stress test varies depending of the severity of AS. For patients with asymptomatic severe AS undergoing stress testing, the incidence of an abnormal stress test has ranged between 28% and 67%, with a pooled average of 49%.[32,35-38,47,55-62] An abnormal response to exercise is thought to reflect poor contractile reserve and an increased transvalvular gradient and Z_{va} during effort.[60,63] Exercise-induced symptoms or an abnormal blood pressure response are also predictive of worse outcome.[41,57,58]

It should be noted that the studies reporting a worse prognosis in patients with an abnormal exercise test have been heterogeneous in terms of exercise protocol (e.g., treadmill vs. bicycle, Naughton vs. Bruce, or other), the definition of what constitutes an abnormal exercise test, study endpoints, and AS severity.[35-38,47,55,57,61] Indeed, the criteria for an abnormal stress test have varied across studies, including limiting symptoms, abnormal blood pressure response (lack of an increase or a drop in blood pressure), ventricular arrhythmias, and ST-segment depression. Some studies have indicated that symptom development during exercise is of greater importance than an abnormal blood pressure response or ST-segment changes; however, these studies were small and heterogeneous, and the optimal criteria for a positive test remain unknown.[6,7,38,39] It is also possible that in these retrospective studies, patients with abnormal stress test results were

followed more carefully, with lower thresholds for AVR referral than those with greater exercise capacity or more normal blood pressure responses. Nonetheless, these studies have consistently shown that prognosis is considerably worse for patients with an abnormal exercise test. A recent meta-analysis by Rafique et al. reported a 6-fold increased risk of cardiac death for patients with an abnormal stress test, with sensitivity, specificity, and positive and negative predictive values of 75%, 71%, 66%, and 79% for adverse cardiac events and 100%, 51%, 5%, and 100% for sudden cardiac death, respectively.[41]

Approximately 15% of patients with asymptomatic AS will not be able to perform an exercise test,[34] a proportion that increases with age.[64]

1.4 Biomarkers in Asymptomatic Severe AS

The ESC/EACTS guidelines note that AVR may be considered in patients with asymptomatic severe AS and markedly elevated levels of natriuretic peptides in the absence of an alternative explanation (Class IIb).[19] N-terminal pro-B-type natriuretic peptide (NT-proBNP) and the active hormone B-type natriuretic peptide (BNP) are released in response to ventricular and/or atrial cardiomyocyte stretch.[65] These biomarkers have prognostic utility in patients with heart failure.[65,66] NT-proBNP levels correlate with AS severity, AVA, V_{max}, and peak gradient.[65,67] In asymptomatic severe AS, baseline BNP levels are predictive of an abnormal blood pressure response to exercise, earlier symptom onset, and mortality.[68-71] One recent study demonstrated that the level of BNP compared to normal reference values (rather than to the absolute value) in patients with moderate-severe AS, both symptomatic and asymptomatic, was associated with excess long-term mortality and that BNP levels added incremental prognostic value to all baseline characteristics.[72] Another study demonstrated the usefulness of measuring BNP during exercise stress test.[73] A higher peak-exercise BNP level was independently associated with a higher occurrence of adverse events (death or AVR) at a mean follow-up of 1.5 years, suggesting an incremental role beyond its resting value. The role and incremental value of novel biomarkers are currently under investigation and could bring meaningful information to better risk stratify asymptomatic patients.[74,75]

1.5 Rationale for the EARLY TAVR Trial

Despite observational studies suggesting benefits of a strategy of early aortic valve replacement in patients with severe but asymptomatic AS compared to active clinical surveillance,[20,22,28,29,75] whether an early intervention will improve outcomes remains unknown and has never been properly studied in a randomized trial. Current guidelines recommend clinical surveillance every 6-12 months, and aortic valve replacement when symptoms occur, or other Class I indication exists such as decrease in LV ejection fraction (LVEF) <50% or the need for other concomitant cardiac surgery.[4] In light of the lack of strong evidence supporting an early aortic valve replacement strategy compared to active clinical surveillance, a randomized trial is justified. Currently a number of randomized studies comparing SAVR and clinical surveillance are planned or ongoing.[76] However, given the less invasive nature and lower rate of peri-procedural mortality and comorbidity, the use of transfemoral TAVR to treat asymptomatic patients may be more appropriate than SAVR and warrants investigation.

The most recent ACC/AHA and European guidelines strongly recommend stress-testing to better clarify patient's symptoms status.[4,19] Low penetration of this recommendation is observed in clinical practice, with approximatively 5-10% of clinicians performing a stress-test when managing asymptomatic severe AS patients.[77] Data from several small retrospective studies suggests worst outcomes for patients with asymptomatic severe AS and abnormal stress-test when managed conservatively compared to a strategy of aortic valve replacement.[41] However, no large and well performed prospective study clearly established the value and role of stress-testing in the evaluation of asymptomatic severe AS. More importantly, while it is estimated that approximatively 50% of patients deemed initially asymptomatic clinically will express some symptoms when challenged on a stress-test, the nature, degree and severity of symptoms and electrocardiographic abnormalities developed during the stress-test and its relationship with future adverse events has never been clearly defined. The purpose of the EARLY TAVR registry is to better understand the incidence of an abnormal stress test, subsequent patient management, and outcomes in these patients.

Bicuspid aortic valve morphology is a common congenital valvular abnormality, occurring in 0.5% to 2% of the general population (89). AS is also a frequent complication in this population and may occur at a younger age in patients with bicuspid valves, when compared with patients with a tricuspid aortic valve morphology (90,91). The pathology involves progressive calcification of the leaflet bodies which limits normal cusp opening during systole. Recent reports on the use of SAPIEN 3 in these patients is feasible and effective with favorable valve performance (92).

2 STUDY OBJECTIVE

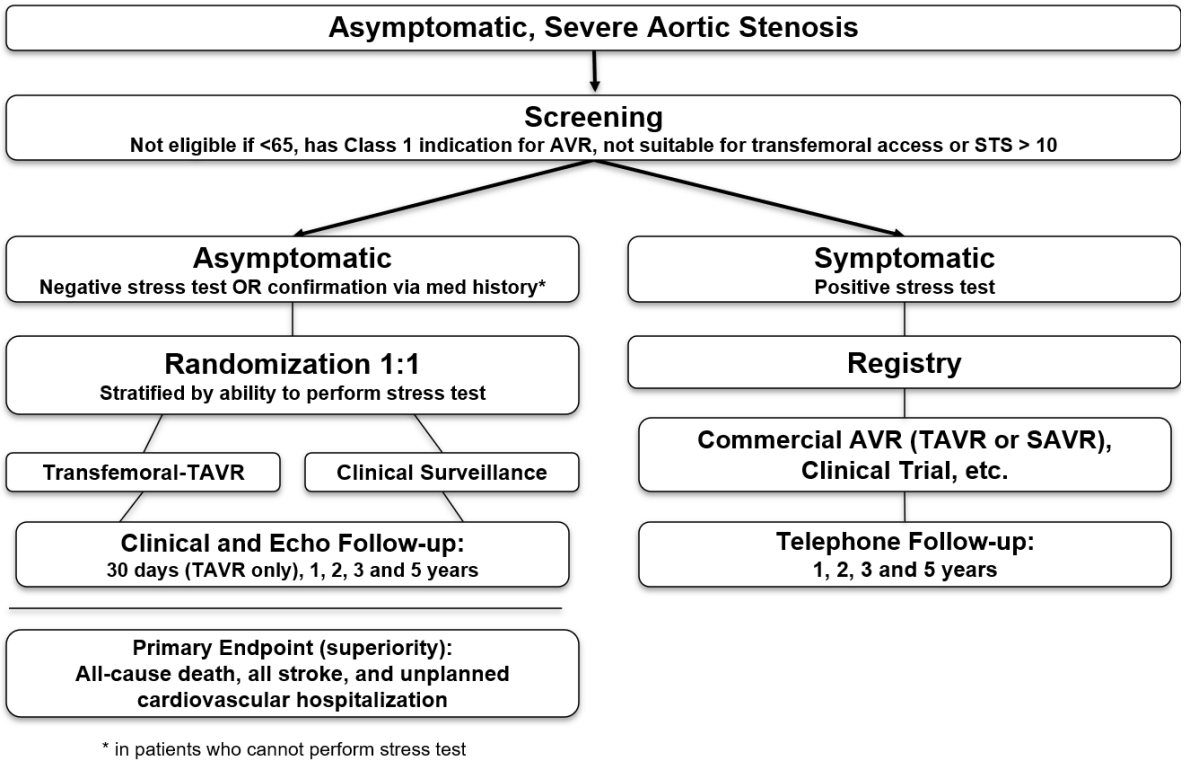
The objective of this study is to establish the safety and effectiveness of the Edwards SAPIEN 3/SAPIEN 3 Ultra Transcatheter Heart Valve (THV) compared with clinical surveillance (CS) in asymptomatic patients with severe, calcific aortic stenosis.

3 STUDY DESIGN

This is a prospective, randomized, controlled, multi-center study. Qualified study patients will be randomized 1:1 to receive either TAVR with the Edwards SAPIEN 3/SAPIEN 3 Ultra THV or clinical surveillance. Patients will be stratified by whether or not they are able to perform a treadmill stress test.

In addition, patients who are screened for enrollment and have a positive stress test will be followed in a registry to collect data on subsequent treatment and mortality, as applicable.

Figure 1. Study Flowchart



4 ENROLLMENT

A total of 900 qualified patients will be enrolled into the study at up to 75 actively enrolling investigative sites in the United States. Additionally, approximately 5-10 sites may be selected outside of the United States. No site will be allowed to enroll more than 15% of patients.

In addition, up to 1000 patients who are not eligible due to a positive stress test will be followed in the EARLY TAVR registry.

Edwards will notify investigative sites of enrollment closure.

5 STUDY DEVICES

The following commercially available devices will be used in the study:

- Edwards SAPIEN 3 THV (Model 9600TFX in 20 mm, 23 mm, 26 mm and 29 mm sizes)
- Edwards SAPIEN 3 Ultra THV (Model 9750TFX in 20 mm, 23 mm, and 26 mm sizes)
- Edwards Commander Delivery System (For use with SAPIEN 3 THV: Models 9600LDS20, 9600LDS23, 9600LDS26, and 9600LDS29; for use with SAPIEN 3 Ultra THV: Models 9750CM20, 9750CM23, 9750CM26)
- Edwards Crimper (Model 9600CR)
- Edwards Expandable Introducer Sheath Set (Models 914ES and 916ES)

5.1 Edwards SAPIEN 3 THV

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

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

The device leaflets are designed to be in the semi-closed configuration at the first heartbeat. The leaflets have a small “cap” at the leaflet tips to accommodate proper coaptation under all deployment configurations (i.e., nominal, under, over and oval). The leaflets are attached via a soft integral tissue tab that is inserted into slots on the frame.

The SAPIEN 3 THV is available in 4 sizes (**Table 3**).

5.2 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.

The SAPIEN 3 Ultra THV is available in three sizes (20, 23, and 26 mm); sizing recommendations are shown below in **Table 3**.

Table 3. Device Sizing

Native Valve Annulus Size (TEE)	Native Valve Annulus Size (CT)		THV Size	Valve Height
	Area	Area Derived Diameter		
16-19 mm	273 – 345 mm^2	18.6-21 mm	20 mm	15.5 mm
18-22 mm	338 – 430 mm^2	20.7-23.4 mm	23 mm	18 mm
21-25 mm	430 – 546 mm^2	23.4-26.4 mm	26 mm	20 mm
24-28 mm	540 – 683 mm^2	26.2-29.5 mm	29 mm	22.5 mm

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.

5.3 Edwards Commander Delivery System

The Commander Delivery System includes:

- Loader
- Qualcrimp Accessory
- 2-piece Crimp Stopper

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

5.4 Loader

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

5.5 Qualcrimp Accessory

The Qualcrimp accessory is a foam tube composed of polyurethane sponge covered in an outer layer of PET. The SAPIEN 3 THV is placed within the Qualcrimp accessory prior to placing it in crimper. The Qualcrimp accessory is intended to protect the leaflets of the THV during crimping.

5.6 Edwards Crimper and 2-piece Crimp Stopper

The Crimper reduces the diameter of the THV to mount it to the delivery system. The Crimper is comprised of a compression mechanism that is closed with a handle located on the housing. The Crimper is used with a 2-piece Crimp Stopper (packaged with the delivery system) to correctly crimp the THV to the appropriate size.

Study devices and components will be used per the Instructions for Use (IFU) and after sufficient training of physicians/site personnel has been achieved as determined by the study sponsor. Further descriptions of these devices are provided in the respective IFUs.

5.7 Device Management

5.7.1 Study Device

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

to the patient.

5.7.2 Device Storage

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

5.7.3 Device Accountability

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

6 STUDY ENDPOINTS

6.1 Primary Safety and Effectiveness Endpoint

The primary safety and effectiveness endpoint is a non-hierarchical composite of all-cause death, all stroke and unplanned cardiovascular hospitalization.

6.2 Secondary Endpoints

The following secondary endpoints will be evaluated in the Intent-to-Treat (ITT) population:

- Composite of 1) alive, 2) Kansas City Cardiomyopathy Questionnaire (KCCQ) score ≥75 and 3) KCCQ decrease ≤10 points at 2 years
- Integrated measure of LV health (LV global longitudinal strain, LV mass index and LA volume index) at 2 years
- Change in LVEF at 2 years
- New onset atrial fibrillation
- Death or disabling stroke

6.3 Additional Safety and Effectiveness Endpoints

The following endpoints will be analyzed in all analysis populations, as applicable. ITT and Per Protocol (PP) analyses will be based on timing post-randomization. Valve Implant (VI) analyses will be based on timing post-procedure.

1. LV global longitudinal strain at 2 years
2. LV mass index at 2 years
3. LA volume index at 2 years

4. Moderate to severe mitral regurgitation at 2 years
5. Death (all cause and cardiovascular) through 1 year and 2 years
6. Stroke (all, disabling and non-disabling) through 1 year and 2 years
7. Death or stroke through 1 year and 2 years
8. Death or disabling stroke through 1 year
9. Unplanned cardiovascular hospitalization through 1 year, 2 years, and 5 years
10. New York Heart Association (NYHA) Functional Class at 2 years
11. Six-minute walk test (6MWT) at 2 years
12. Health status as evaluated by Quality of Life (QoL) questionnaires
    - KCCQ at 2 years
    - EQ-5D-5L at 2 years
    - 36-item Short Form Health Survey (SF-36) at 2 years

The following additional endpoints will be also assessed post-procedure in the Valve Implant (VI) population:

1. Death or stroke through 30 days
2. New onset atrial fibrillation through 30 days,1 year and 2 years
3. Composite of 1) alive, 2) KCCQ score ≥75 or 3) KCCQ decrease ≤10 points at 1 year and 2 years
4. NT pro-BNP at 30 days
5. Major vascular complications through 30 days
6. Bleeding complications at 30 days
7. Myocardial infarction through 30 days
8. Acute kidney injury through 30 days
9. Coronary obstruction requiring intervention through 30 days
10. New permanent pacemaker implantation resulting from new or worsened conduction disturbances through 30 days
11. Unplanned cardiovascular hospitalization through 30 days
12. LVEF at 30 days, 1 year and 2 years
13. LV global longitudinal strain at 30 days and 1 year
14. LV mass index at 30 days and 1 year
15. LA volume index at 30 days and 1 year
16. Integrated measure of LV health at 30 days, 1 year and 2 years

17. Moderate to severe mitral regurgitation at 30 days and 1 year
18. Hemodynamic valve performance evaluation by echocardiography for aortic valve stenosis and aortic valve regurgitation (paravalvular and central) at 30 days, and 1 year, 2 years and 5 years
19. Structural valve deterioration at 1 year, 2 years and 5 years
20. Length of hospital stay, ICU days and discharge location
21. NYHA Functional Class at 30 days and 1 year
22. 6MWT at 30 days and 1 year

7 STUDY POPULATION

The study population will be comprised of patients with asymptomatic, severe, calcific aortic stenosis with appropriate anatomy for transfemoral TAVR with SAPIEN 3/SAPIEN 3 Ultra.

7.1 Inclusion Criteria

Patients must meet the following inclusion criteria to be included in the trial:

1. 65 years of age or older at time of randomization
2. Severe AS defined as:
   - AVA ≤1.0 cm^2 or AVA index ≤0.6 cm^2/m^2 AND
   - Peak jet velocity ≥4.0 m/s or Mean gradient ≥40 mmHg
3. Patient is asymptomatic defined as:
   1) Negative treadmill stress test. To be considered asymptomatic, the patient must not demonstrate any of the following during and/or after the test:
      - Syncopal or pre-syncopal episode, including severe dizziness
      - Angina
      - Limiting dyspnea or decreased exercise tolerance, defined as inability to reach 60% of age and sex adjusted metabolic equivalents of task (METs)
      - Drop in systolic blood pressure (defined as a progressive drop of at least 20 mmHg and sustained for 1 minute or an acute drop of 40 mmHg)
      - Significant ventricular arrhythmias (≥4 consecutive ventricular premature beats)

   OR

   2) Per physician after thorough assessment of patient history if the patient is unable to perform a stress test.
4. LV ejection fraction ≥50%

5. Society of Thoracic Surgeons (STS) risk score ≤10
6. The study patient has been informed of the nature of the study, agrees to its provisions and has provided written informed consent as approved by the institutional review board (IRB) of the respective clinical site.

7.2 Exclusion Criteria

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

1. Patient is symptomatic (e.g., NYHA Functional Class ≥2, history of syncopal episode, or CCS angina score >1, hospitalization for heart failure within the last 12 months).
2. Patient has any concomitant valvular, aortic, coronary artery disease requiring surgery making AVR a Class I indication.
3. Native aortic annulus size unsuitable for sizes 20, 23, 26, or 29 mm THV based on 3D imaging analysis
4. Iliofemoral vessel characteristics that would preclude safe placement of the introducer sheath.
5. Left ventricular outflow tract calcification that would increase the risk of annular rupture or significant paravalvular leak (PVL) post TAVR
6. Evidence of an acute myocardial infarction ≤30 days before randomization
7. Aortic valve is unicuspid, bicuspid with unfavorable features for TAVR (e.g., aneurysmal ascending aorta, i.e., >4.0 cm; severe or bulky calcification of the LVOT or raphe that would increase the risk of annular injury or significant PVL post TAVR; coronary anatomy that increases the risk of coronary artery obstruction post TAVR), or is non-calcified
8. Severe aortic regurgitation (>3+)
9. Severe mitral regurgitation (>3+) or ≥moderate mitral stenosis
10. Pre-existing mechanical or bioprosthetic valve in any position. (Of note, mitral ring is not an exclusion)
11. Symptomatic carotid or vertebral artery disease or successful treatment of carotid stenosis within 30 days of randomization
12. 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
13. Hemodynamic or respiratory instability requiring inotropic support, mechanical ventilation or mechanical heart assistance within 30 days of randomization
14. Hypertrophic cardiomyopathy with obstruction
15. Cardiac imaging (echo, Computed Tomography (CT), and/or Magnetic Resonance Imaging (MRI)) evidence of intracardiac mass, thrombus or vegetation
16. Inability to tolerate or condition precluding treatment with anti-thrombotic therapy

17. Stroke or transient ischemic attack (TIA) within 90 days of randomization
18. Renal insufficiency (estimated glomerular filtration rate (eGFR) <30 mL/min per the Cockcroft-Gault formula) and/or renal replacement therapy
19. Active bacterial endocarditis within 180 days of randomization
20. Severe lung disease (FEV1 <50% predicted) or currently on home oxygen
21. Severe pulmonary hypertension (e.g., pulmonary artery (PA) systolic pressure ≥2/3 systemic pressure)
22. History of cirrhosis or any active liver disease
23. Significant frailty as determined by the Heart Team (after objective assessment of frailty parameters)
24. Significant abdominal or thoracic aortic disease (such as aneurysm, severe calcification, aortic coarctation, etc.) that would preclude safe passage of the delivery system
25. Patient refuses blood products
26. BMI >50 kg/m^2
27. Estimated life expectancy <24 months
28. Absolute contraindications or allergy to iodinated contrast that cannot be adequately treated with pre-medication
29. 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.
30. Active SARS-CoV-2 infection (Coronavirus-19 [COVID-19]) or previously diagnosed with COVID-19 with sequelae that could confound endpoint assessments (as assessed by Case Review Board)

8 STUDY PROCEDURES

8.1 Screening Period

The screening period is designed to obtain patient consent, determine patient eligibility for the study, and to submit for case review. The screening assessments will occur within the 30 days prior to randomization, unless otherwise noted. All patients that sign an informed consent will be entered into the electronic data capture (EDC) system and be assigned a Subject ID.

Patients that have signed the informed consent and do not meet the eligibility criteria in **Sections 7.1** and **7.2** will be considered a Screen Failure (SF).

The following information will be collected as part of Screening:

Consent:

- Patient informed consent completion (**Section 8.1.1**)

Risk Assessment:

- STS Risk Score

Systems:

- Medical history and physical assessment (including height, weight, blood pressure and heart rate)
- Medications including heart failure medications and antithrombotics

Cardiopulmonary:

- Symptom Status
  - Treadmill Stress Test
    - Conducted to assess the occurrence of exercise-induced symptoms (angina, pre-syncopal or syncopal episode, test-limiting dyspnea) blood pressure response, the occurrence of new arrhythmias, and patient's functional capacity (oxygen consumption and METs). Treadmill stress test performed 90 days prior to randomization may be accepted per investigators' discretion if patient is still clinically asymptomatic.
    - The appropriate treadmill protocol (Modified Bruce, Naughton or Bruce Treadmill Stress Test Protocol) will be selected per investigator discretion according to patient's age, functional status, and other clinical characteristics.
    - The treadmill stress test should be discontinued once 100% expected METs is achieved.
  - For patients who are unable to perform a treadmill stress test, a thorough assessment of the patient's history should be conducted to determine whether the patient has experienced any symptoms or events that are likely attributable to AS.
- NYHA Functional Class

- Canadian Cardiovascular Society (CCS) status of angina
- Comprehensive transthoracic echocardiogram (TTE), including assessment of aortic valve gradients (mean and peak), areas, indices, degree of regurgitation, left ventricle systolic function (global and segmental). Qualifying TTE must be performed within 90 days prior to randomization.
- 3D Cardiac imaging (Transesophageal Echocardiogram (TEE), CT or cardiac MRI) with 3D reconstruction to determine aortic valve annulus area. Qualifying cardiac imaging must be performed within 1 year prior to randomization
- CT Angiography, including thoracic and abdomen scan with visualization of iliac and femoral arteries. Qualifying CT must be performed within 1 year prior to randomization
- Assessment of severity of coronary artery disease (CAD) may be performed by CTA (preferred) 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 randomization.
    - If the CAD assessment by CTA is suboptimal or inconclusive, but does not show any sign of significant proximal CAD and there is no patient history of CAD, coronary angiography may be deferred until the TAVR procedure.

Clinical Laboratory Tests:

- WBC, Hgb, and platelet count
- PT or INR
- Creatinine
- eGFR
- Albumin
- SARS-CoV-2 viral test

Functional Assessments:

- Heart Team assessment of frailty

8.1.1 Informed Consent

The study investigator(s) and support staff will approach patients with severe, calcific aortic stenosis who are asymptomatic to assess their interest in participating in the study by providing them an overview of the study including the background, risks, benefits and study procedures. If patients are interested in participating in the study, including the registry if applicable, the study patient will sign the IRB-approved informed consent form (ICF) prior to any study specific procedures being performed. All patients consented should be entered into the study's EDC

system.

8.1.2 Case Review

The Case Review Board is comprised of a subset of Investigators who are participating in the trial. The role of the Case Review Board is to review submitted cases to determine if the patient is an appropriate candidate for the trial, with a focus on confirming the patient's asymptomatic status, operative risk, valve sizing, appropriate vascular access and any relevant clinical factors impacting enrollment eligibility. Before a case is submitted for review, the site Principal Investigator and Heart Team will screen the patient for fundamental enrollment criteria. Once fully screened and deemed an appropriate candidate, the site will submit the case for review and approval consideration by the Case Review Board. Once a case is approved by the Case Review Board, the patient will be eligible for randomization. The Sponsor will maintain a record of the case presentation and case approval notes.

8.2 Randomization

Randomization will be done 1:1 for test and control and will be stratified by site and ability to perform a stress test at baseline. To randomize a patient, the investigative site will enter the subject into the designated electronic system and obtain the treatment assignment (TAVR or Clinical Surveillance). Once the assignment has been made the subject will be considered randomized into the study.

All randomized patients will be considered part of the ITT population. Randomized patients are considered enrolled in the study.

8.3 Baseline Assessments

In addition to the Screening Assessments, the following Baseline data will be collected for patients with a negative treadmill stress test or confirmed to be asymptomatic via medical history. Baseline assessments should be performed within 30 days post randomization or prior to the procedure whichever comes first. Baseline and Screening assessments can be collected in the same visit, as appropriate.

Risk Assessment:

- EuroSCORE II

Cardiopulmonary:

- 12-lead Electrocardiogram (ECG)
- SYNTAX Score (only for patients with significant native coronary artery disease (CAD))
- Pulmonary Function Test for patients with a history of lung disease

Clinical Laboratory Tests:

- AST/ALT (required for patients with chronic liver disease)
- Sample collection for Biomarker assessment should be performed before or at least 12

hours after (preferable) the treadmill stress test, if applicable.

Neurological Assessments:

- National Institutes of Health Stroke Scale (NIHSS)
- Modified Rankin Scale (mRS)

Functional and Quality of Life Assessments:

- 6MWT
- QoL
  - KCCQ
  - EQ-5D-5L
  - SF-36

8.4 Procedure

For patients randomized to the TAVR arm, every effort should be made to have the valve implant procedure occur within 14 days of randomization. The valve implant procedure will be considered to have started when the first interventional access related puncture (venous or arterial) is established. Performance of TEE does not by itself constitute start of procedure.

Valve implant procedure assessments will include the following:

Systems:

- Medications including all heart failure medications and antithrombotics
- Adverse event assessment

Cardiopulmonary:

- TTE and supra-aortic angiogram
  or
- TEE

Study patients will be continuously monitored clinically, hemodynamically, and electrocardiographically during catheterization for all local, systemic side effects and complications. If the procedure is aborted (prior to or after the start of the valve implant procedure), the procedure may be re-scheduled if the patient continues to meet all inclusion/exclusion criteria.

8.4.1 Device Preparation

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

8.4.2 Antithrombotic Recommendations

Table 4 outlines the recommended anticoagulation/antiplatelet regimen for patients undergoing TAVR. The categories were developed by The PARTNER II Trial Patient and Procedure

Management Steering Committee. There are no current validated guidelines in this specific study population, however, the literature was surveyed and used as guidance for the following proposed guidelines.[78]

Table 4. Recommended Antithrombotic Regimen

Pre-procedure	
• Aspirin 81-100 mg QD • Patients with BMS within one month or DES within 12 months should be continued on antiplatelet therapy prior to their implant procedure • Patients in atrial fibrillation on oral anticoagulants should be bridged with LMW or UF heparin prior to the implant procedure according to their stroke risk • Patients with persistent or paroxysmal atrial fibrillation, not on anticoagulation, will not be required to have a TEE to rule out LA thrombus prior to implant procedure. If intra-procedural TEE during TAVR reveals thrombus, implant procedure will be aborted and delayed until patient has been on warfarin or dabigatran for 30 days. Note: thrombus must be eliminated in order to proceed with TAVR. • In patients undergoing concomitant TAVR/PCI, clopidogrel loading with either 300mg or 600mg prior to the implant procedure is recommended in addition to ASA	
Intraprocedural	
Heparin will be given to achieve/maintain ACT ≥ 250 sec.	
Post-procedure	
Category I for Stroke Risk No atrial fibrillation, No recent stents	• ASA 81mg QD • Clopidogrel 300mg load within 6 hours of the implant procedure (either pre or post) • Clopidogrel 75mg 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 prior to the implant procedure and after the implant procedure without interruption for at least one month after BMS and 6-12 months after DES
Category III for Stroke Risk Atrial fibrillation, no recent stents	• ASA 81 mg QD • Patients should be started on oral anticoagulants 24 hours post TAVR if clinically safe and this should be continued for at least one month or indefinitely if possible. If clinically safe, patients started on warfarin should be bridged with unfractionated or low molecular weight heparin until INR therapeutic. • If patients are not a candidate for oral anticoagulants, 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 • Patients should be started on oral anticoagulants 24 hours post TAVR if clinically safe and continued indefinitely. If clinically safe, patient's being started on warfarin should be bridged with UF or LMW heparin until INR therapeutic.

8.4.3 Antibiotic Prophylaxis

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

8.4.4 Contrast Media

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

8.4.5 Radiation Precautions

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

Radiation exposure of 6-15 mSv is estimated for the Screening CT.[79] If a radiation induced skin injury is suspected, the Investigator must report an adverse event and assess and treat the patient as medically necessary.

8.5 Post TAVR

The post procedure time period is defined as the 48 hours after the patient exits the cath lab/operating room. Subsequent monitoring will continue according to institutional standard of care.

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

Systems:

- Medications including heart failure medications and antithrombotics.
- Adverse event assessment

Cardiopulmonary:

- 12-lead ECG

Clinical Laboratory Tests:

- WBC, Hgb, and platelet count
- Creatinine

Neurological assessments:

- NIHSS, if symptoms of stroke are suspected

8.6 Discharge

For patients discharged within 48 hours of exiting the cath lab / operating room, it is not required to repeat tests collected during the Post Procedure period that are also required for the discharge visit. If the patient was discharged over a weekend or holiday, the discharge assessments may

be completed on the last weekday prior to discharge.

The following information will be collected for study patients within 24 hours of the date and time of discharge.

Systems:

- Physical assessment including weight, blood pressure, and heart rate
- Medications including heart failure medications and antithrombotics
- Adverse event assessment

Cardiopulmonary:

- NYHA functional class
- CCS Angina
- Comprehensive TTE

Clinical Laboratory Tests:

- WBC, Hgb and platelet count
- PT or INR for patients receiving warfarin
- Creatinine

Neurological Assessments:

- NIHSS, if symptoms of stroke are suspected

8.7 30-Day Post Procedure

Patients should be assessed 30-days post procedure. The visit window is +7 days and is calculated from the date of the procedure.

The following data will be collected:

Systems:

- Physical assessment including weight, blood pressure, and heart rate
- Medications including heart failure medications and antithrombotics.
- Adverse event assessment

Cardiopulmonary:

- NYHA functional class
- CCS Angina
- Comprehensive TTE
- 12-lead ECG

Clinical Laboratory Tests:

- WBC, Hgb, and platelet count
- Creatinine
- Sample collection for Biomarker assessment

Neurological Assessments:

- NIHSS
- mRS

Functional Assessments:

- 6MWT
- QoL
  - KCCQ
  - EQ-5D-5L
  - SF-36

8.8 Years 1, 2 and 3

All patients will be assessed at Years 1, 2 and 3. The visit window is +30 days and is calculated from the date of randomization for patients in the Clinical Surveillance arm, and from the date of the procedure for patients in the TAVR arm.

The following data will be collected:

Systems:

- Physical assessment including weight, blood pressure, and heart rate
- Medications including heart failure medications and antithrombotics.
- Adverse event assessment

Cardiopulmonary:

- 12-lead ECG
- NYHA functional class
- CCS Angina
- Comprehensive TTE

Clinical Laboratory Tests:

- Sample collection for biomarker assessment – only at years 1 and 2 for patients in CS arm who have not had AVR

Functional Assessments:

- 6MWT
- QoL
  - KCCQ
  - EQ-5D-5L
  - SF-36

8.9 Year 5

All patients will be assessed at Year 5. The five-year visit window is +45 days and will be calculated from the date of randomization for patients in the Clinical Surveillance arm, and from the date of the procedure for the patients in the TAVR arm.

The following data will be collected:

Systems:

- Physical assessment including weight, blood pressure and heart rate
- Medications including heart failure medications and antithrombotics.
- Adverse event assessment

Cardiopulmonary:

- NYHA functional class
- CCS Angina
- Comprehensive TTE

Functional Assessments:

- QoL
  - KCCQ
  - SF-36

8.10 Years 7 and 10

All patients randomized to the Clinical Surveillance arm who remain asymptomatic and have not undergone AVR at the time of the 5-year visit will be contacted by phone at Years 7 and 10 to assess AVR status and survival.

8.11 Delayed AVR in Clinical Surveillance Arm

It is anticipated that a proportion of patients who are randomized to the Clinical Surveillance arm will develop symptoms or other indications necessitating AVR during the follow-up period. It is

expected that patients will undergo transfemoral TAVR using the devices provided for the study unless other treatment is necessary (e.g., patient is no longer anatomically appropriate, patient treated urgently at a non-EARLY TAVR site, etc.). The events that led to the decision to perform AVR will be documented. Patients undergoing delayed AVR will have the following Screening and Baseline assessments repeated within 30 days prior to the procedure. If a patient undergoes AVR urgently and/or at a non-EARLY TAVR site, every effort should be made to obtain admission history and physical, index procedure report and discharge from index hospitalization along with relevant echocardiographic reports from the treating facility.

Risk Assessment:

- STS Risk Score
- EuroSCORE II

Systems:

- Physical assessment (including height, weight, blood pressure and heart rate).
- Medications including heart failure medications and antithrombotics.
- Adverse event assessment

Cardiopulmonary:

- NYHA functional class
- CCS angina
- Comprehensive TTE
- 3D Cardiac imaging (TEE, CT, or cardiac MRI) *
- CT Angiography, including thoracic and abdomen scan with visualization of iliac and femoral arteries. *
- Assessment of CAD*
- 12-lead ECG
- SYNTAX Score (for patients with significant native CAD)

*Whether the assessment should be repeated is at the Investigator's discretion

Clinical Laboratory Tests:

- WBC, Hgb and platelet count
- PT or INR
- Creatinine
- eGFR
- Albumin
- Sample collection for Biomarker assessment

Neurological Assessments:

- NIHSS
- mRS

Functional and Quality-of-Life Assessments:

- Heart Team assessment of frailty
- 6MWT
- QoL
  - KCCQ
  - EQ-5D-5L
  - SF-36

In addition, the following assessments will be performed according to the schedule for the TAVR arm as follows:

- Procedure (**Section 8.4**)
- Post-Procedure (**Section 8.5**)
- Discharge (**Section 8.6**)
- 30-Day Post-Procedure (**Section 8.7**)
- Years 1, 2 and 3 Post-Procedure (**Section 8.8**)
- 5-Year Post-Procedure (**Section 8.9**)

If the patient undergoes AVR prior to Year 2, a 2-year post-randomization visit will be conducted in addition to the Year 2 post-procedure visit. All assessments in **Section 8.8** will be performed at these visits.

If the visit windows for any post-procedure visit and the 2-year post-randomization visit are within 30 days of each other, assessments only need to be performed once and should be performed within the latest visit window.

8.12 Neurological Assessments

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

Following the procedure, all subjects should be assessed to determine if there is evidence of neurological impairment. If symptoms of a stroke are suspected, the NIHSS should be performed. For all subjects diagnosed with a new stroke after the procedure start, a follow-up mRS assessment should be performed 90 days (± 30 days) after stroke onset to assess stroke disability

(visit or phone assessment is acceptable). If the 90-day post-stroke assessment is scheduled to occur within 30 days of the next protocol-specified visit, the mRS does not need to be repeated.

8.13 QoL Questionnaires

QoL will be measured through the following standard surveys:

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

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

Investigational staff will administer patient questionnaires to study patients. Patients will be instructed to complete each questionnaire at visits specified in **Section 8**. Investigational sites should retain the completed questionnaire in the patients' source documents.

8.14 COVID-19 Assessments

In addition to the testing performed during the screening period, if a patient has an endpoint-related event, additional testing may be requested. Results of all available COVID-19 testing should be recorded in the CRFs.

8.15 EARLY TAVR Registry

Patients who are not eligible for randomization due to a positive treadmill stress test (i.e., symptomatic) will be followed in a registry. The following information will be collected as part of screening/baseline in addition to patient informed consent completion (**Section 8.1.1**) and treadmill stress test (**Section 8.1**). The screening assessments will occur prior to subsequent treatment for severe aortic stenosis, preferably within 30 days of the treadmill stress test.

Risk Assessment:

- STS Risk Score

Systems:

- Medical history and physical assessment (including height, weight, blood pressure and heart rate)
- Medications including heart failure medications and antithrombotics

Cardiopulmonary:

- NYHA Functional Class
- Comprehensive TTE. Qualifying TTE must be performed within 90 days of the treadmill stress test or prior to the subsequent treatment, whichever comes first.

Clinical Laboratory Tests:

- If possible, collect the Biomarker sample (optional). Sample collection for Biomarker assessment should be performed before or at least 12 hours after (preferable) the treadmill stress test for these patients. If collected, the Biomarker collection must occur prior to subsequent treatment for severe aortic stenosis.

The patient's subsequent treatment (e.g., SAVR or TAVR in the commercial setting, enrollment in PARTNER 3, clinical surveillance, etc.) will be documented. In addition, patients will be contacted by phone at Years 1, 2, 3 and 5 to assess vital status, if unknown.

8.16 Patient Discontinuation

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

Site personnel should make all reasonable efforts to locate and communicate with the subject at each visit time point. If a subject is unable to return to the clinic for a protocol-required visit, the subject should be contacted via preferred remote method (telemedicine, etc.) to complete as many assessments as possible; subjects should be rescheduled to complete the remaining assessments as soon as reasonably possible. For each missed visit, multiple attempts to contact the subject should be made and details recorded in the source documentation. A subject is not considered lost to follow-up until the full follow-up period has elapsed.

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

Table 5. Schedule of Assessments

	All Patients		TAVR Arm						Clinical Surveillance Arm			
Event	**Screening**	**Baseline[1]**	**Procedure[2]**	**Post-procedure[2]**	**Discharge[2]**	**30 days post-procedure (+7 days) [2]**	**1, 2, 3 years post-procedure (+30 days)**	**5 years post-procedure (+45 days)**	**1, 2, 3 year post-randomization (+30 days)**	**5 years post-randomization (+45 days)**	**7, 10 years post-randomization (+45 days)**	**Pre-procedure[3]**
Informed Consent	X[20]											
Treadmill Stress Test	X[20]											
STS Risk Score	X[20]											X
Medical History	X[20]											
Physical Assessment	X[20]				X	X	X	X	X	X		X
Medications	X[20]		X	X	X	X	X	X	X	X		X
NYHA Functional Class	X[20]				X	X	X	X	X	X		X
CCS Angina	X				X	X	X	X	X	X		X
Comprehensive TTE	X[4,20]		X[5]		X	X	X	X	X	X		X
3D Cardiac Imaging [6]	X											X
CT Angiography [7]	X											X
Assessment of CAD	X [8]											X
WBC, Hgb, Platelet Count	X			X	X	X						X
PT or INR	X				X[21]							X
Creatinine	X			X	X	X						X
eGFR	X											X
SARS-CoV-2 viral test [9]	X											
Frailty Assessment (including Albumin) [10]	X											X

	All Patients		TAVR Arm						Clinical Surveillance Arm			
Event	**Screening**	**Baseline[1]**	**Procedure[2]**	**Post-procedure[2]**	**Discharge[2]**	**30 days post-procedure (+7 days) [2]**	**1, 2, 3 years post-procedure (+30 days)**	**5 years post-procedure (+45 days)**	**1, 2, 3 year post-randomization (+30 days)**	**5 years post-randomization (+45 days)**	**7, 10 years post-randomization (+45 days)**	**Pre-procedure[3]**
Case Review	X											
Sample collection for Biomarker assessment		X[11,20]				X			X[12]			X
EuroSCORE II		X										X
ECG		X		X		X	X		X			X
SYNTAX Score[13]		X										X
Pulmonary Function Test[14]		X										
AST/ALT[15]		X										
NIHSS[16]		X		X[17]	X[17]	X						X
Modified Rankin Scale[16,18]		X				X						X
6-minute Walk Test		X				X	X		X			X
KCCQ		X				X	X	X	X	X		X
EQ-5D-5L		X				X	X		X			X
SF-36		X				X	X	X	X	X		X
Adverse Events		X	X	X	X	X	X	X	X	X		X
Telephone contact[19]											X	

1 For patients randomized to the TAVR arm, assessments should be performed within 30 days prior to the procedure unless otherwise noted. Baseline and Screening assessments can be collected in the same visit, as appropriate.

2 Patients randomized to the CS arm who subsequently undergo AVR will be followed according to the schedule for the TAVR arm. If the patient undergoes AVR prior to

Year 2, the Year 2 post-randomization visit will also be conducted. If the visit windows for any post-procedure visit and the 2-year post-randomization visit are within 30 days of each other, assessments only need to be performed once and should be performed within the latest visit window.

3 Only for patients initially randomized in the CS arm who subsequently undergo AVR during follow-up; assessments will be conducted within 30 days prior to the procedure.
4 Qualifying echocardiogram must have been performed within the 90 days prior to randomization.
5 TTE/supra aortic angiogram or TEE on date of valve implant procedure.
6 TEE, CT or cardiac MRI with 3D reconstruction to determine aortic valve annulus area. Must be performed within 1 year prior to randomization.
7 Including thoracic and abdomen scan with visualization of iliac and femoral arteries. Must be performed within 1 year prior to randomization
8 Assessment of severity of CAD may be performed by CTA (preferred) 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 randomization. If the CAD assessment by CTA is suboptimal or inconclusive but does not show any sign of significant proximal CAD and there is no patient history of CAD, coronary angiography may be deferred until the TAVR procedure.
9 In addition to the testing performed during the screening period, if a patient has an endpoint-related event, additional SARS-CoV-2 testing may be requested. Results of all testing should be recorded on the CRFs.
10 Frailty assessment by the Heart Team
11 Should be collected before or at least 12 hours after (preferable) the treadmill stress test.
12 Sample to be collected at 1 and 2 years only if no AVR
13 Only for patients with significant CAD.
14 Only for patients with a history of lung disease.
15 Only required for patients with chronic liver disease.
16 Every effort should be made to have a neurologist (or neurology fellow) perform the NIHSS and mRS. If it is not possible to have the neurologist/fellow perform the assessments within the protocol-specified visit window, a certified study team member may perform the assessments.
17 Following the procedure, all subjects should be assessed to determine if there is evidence of neurological impairment. If symptoms of a stroke are suspected, the NIHSS should be performed.
18 For all subjects diagnosed with a new stroke after the procedure start, a follow-up mRS assessment should be performed 90 days (± 30 days) after stroke onset to assess stroke disability (visit or phone assessment is acceptable). If the 90-day post-stroke assessment is scheduled to occur within 30 days of the next protocol-specified visit, the mRS does not need to be repeated.
19 Patients randomized to the CS arm who remain asymptomatic and have not undergone AVR at the 5-year visit will be contacted by telephone to determine survival and assess status of aortic valve intervention
20 Screening/baseline assessments of patients in the EARLY TAVR Registry.
21 Only for patients receiving warfarin

9 ADVERSE EVENTS

9.1 Adverse Event

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

Adverse events may be volunteered by patients, elicited or collected via observation by the Investigator or designee or discovered by review of clinical records by the Clinical Events Committee (CEC), Edwards Safety team or Edwards Monitoring team.

In addition, patients will be instructed to contact the investigator, and/or study coordinator if any significant adverse events occur between study visits. If it is determined that an AE has occurred, the investigator should obtain all the information required to complete the AE Form of the electronic Case Report Form (CRF). All AEs will be assessed by the Investigator who will determine whether or not the event is related to the device and/or implant procedure, and whether or not the event meets seriousness criteria.

All relevant AEs will be reported by the Investigator and reviewed by the Sponsor in compliance with applicable regulations as indicated below **Section 9.5**.

9.2 Serious Adverse Event

An Adverse Event is considered serious if the event:

- Led to death;
- Led to a serious deterioration in the health of the study patient that:
  - Resulted in life-threatening illness or injury;
  - Resulted in a permanent impairment of a body structure or a body function;
  - Required inpatient hospitalization or prolongation of existing hospitalization;
  - Resulted in medical or surgical intervention to prevent permanent impairment to body structure or a body function;
- Led to fetal distress, fetal death or congenital abnormality or birth defect;
- Significant medical event: Important medical events that do not meet the above criteria may still be considered SAEs if they seriously jeopardize the patient and require immediate medical or surgical intervention to prevent one of the aforementioned outcomes.

9.3 Anticipated Adverse Events

Anticipated adverse events are AEs that have been identified as possible adverse events related to the investigational device or implant procedure (see **Section 10.2**)

9.4 Unanticipated Adverse Device Effect

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

The Investigator is also responsible for notifying his/her IRB and the Sponsor of all UADEs occurring at his/her site as soon as practical but no later than 10 working days after the investigator first learns of the effect and submitting any additional information as required by IRB, local regulations, Sponsor or Food and Drug Administration (FDA).

All UADEs must be followed until resolution or until a stable clinical endpoint is reached. All required treatments and outcomes of the UADEs must be recorded in the study database.

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

9.5 AE Reporting Requirements

All relevant AEs will be captured from the time of randomization (enrollment) until the study patient's participation has ended (i.e. completion of study or discontinuation). 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 adverse event but should be reflected as an outcome to another specific AE.

AEs and/or SAEs should be reported as soon as practical but no later than 10 working days of the site awareness of these events. Adverse events must be followed until resolution, stabilization or study completion.

AE information must be entered into the EDC. When EDC system is not available/accessible, AE information must be reported directly via email to THV_Safety@edwards.com, copying the Safety Officer of the study.

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

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

- Aware date

The site will provide a copy of supporting documentation (example: admission H&P, implant procedure reports, anesthesia records, discharge summary, echocardiogram and ECG reports, laboratory results, etc.) for all endpoint related events, device malfunctions, device and procedure related events, and UADEs to Edwards Lifesciences (or designee). Source documentation will also be requested by the Sponsor for other AEs that may meet potential complaint reporting criteria in order to verify that events are being assessed appropriately.

For patients undergoing TAVR, enrolling sites must provide to the Sponsor at a minimum an admission history and physical, implant procedure report, discharge summary and relevant echocardiographic reports. This will be done irrespective of subject having any AE/SAE during the implant hospitalization.

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

9.5.1 Events that do not require reporting to the Sponsor:

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

- Post-operative pain.
- Post-anesthesia emesis, nausea or headache (within 24 hours of procedure).
- Electrolyte imbalance without clinical sequelae following procedure, even if requiring correction.
- Low grade temperature increase (≤101°F or 38.5°C).
- 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.

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

9.6 Causality of AEs

For each AE, the Investigator will determine whether the event is related to the device and/or the implant procedure, and whether the event meets the definition of a SAE or UADE as outlined in **Sections 9.2** and **9.4**.

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

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

9.7 Sponsor Assessment of AEs

All AEs will be reviewed by the Medical 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, (based on the list of potential risks provided in **Section 10.2**), and whether it qualifies as an SAE.

9.8 Device Malfunctions

A device malfunction is defined as the failure of a device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling of the device. The intended performance of a device refers to the intended use for which the device is labeled or marketed. Device malfunctions should be reported to the Sponsor as soon as practical but no later than 10 working days of the site awareness of these malfunctions.

10 RISKS AND BENEFIT ANALYSIS

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

10.1 Potential Benefits

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

10.2 Potential Risks

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

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

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

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

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

Potential risks associated with Clinical Surveillance include but are not limited to:

- Sudden death
- Rapid deterioration of left ventricular function
- Irreversible myocardial damage with worsened prognosis
- The appearance of symptoms may require an urgent need for TAVR/AVR
- Increased operative risk (e.g., with increased patient age, worsening LV dysfunction and development of comorbidities)

10.2.1 Risk Minimization

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

Additionally, efforts will be made to minimize risks through site/investigator selection and management. First, site and investigator selection criteria are established to ensure that the study personnel and their institutions are qualified to screen, perform and manage the study procedures

as well as support the associated requirements for research. Second, the trial management structure is designed to provide disciplined oversight of the trial activities including close monitoring of site and personnel performance and also support opportunities for investigators and study personnel to share best practices through investigator meetings, ongoing education and case reviews.

The SAPIEN 3 THV represents a third generation THV for Edwards Lifesciences and was developed with the experience from the first and second generation SAPIEN THVs. The SAPIEN 3 System has undergone extensive clinical testing in the aortic position and is commercially available in 53 countries including the US and the 28 EU member states for TAVR in patients with symptomatic, severe aortic stenosis who are at low or higher surgical risk.

The SAPIEN 3 Ultra System is commercially available.

11 STATISTICAL CONSIDERATIONS

11.1 Sample Size Justification

The primary endpoint will be evaluated in the ITT population and will be compared between trial arms using the log-rank test. All events post-randomization will be considered.

The cumulative event rate was determined based on preliminary aggregate data and was fitted assuming the Weibull distribution. Assuming a 10% attrition rate over 2 years and under two-sided log-rank test at alpha = 0.05, a sample size of 900 patients with equal assignment between two groups will yield a study power greater than 85% if the 2-year difference between the groups is ≥ 7%.

The analysis will be performed when at least 271 events are observed (projected to occur when all patients reach two years follow-up).

11.2 Randomization

Randomization will be 1:1 for test and control and will be stratified by site and ability to perform a stress test at baseline. The number of patients who are unable to perform the stress test will be capped at 30% of the total randomized population (270 patients). To randomize a patient, the investigative site will enter the subject into the designated electronic system and obtain the treatment assignment (TAVR or CS). Once the assignment has been made the subject will be considered randomized into the study.

All randomized patients will be considered part of the ITT population. Randomized patients are considered enrolled in the study.

11.3 Analysis Populations

- The Intent to Treat (ITT) population consists of all randomized patients, analyzed in their randomized trial arms. This population is the primary population for trial arm comparisons.

- The Per Protocol (PP) population is the subset of the ITT population excluding the following patients:
    - Randomized Test patients who do not receive the TAVR procedure with a study valve.
    - Randomized Control patients who withdraw from the trial without any clinical data other than baseline being available.
    - Randomized Control patients who undergo surgical AVR or who receive any THV other than a study valve.

  Selected trial arm comparisons will be repeated in this population. If the excluded groups above are only a small proportion of the overall population, only the primary endpoint and its components will be evaluated in the PP population.
- The Valve Implant (VI) population consists of all patients in either trial arm who receive and retain a study valve. This population will be used for echo analyses, and other analyses as applicable.

It is anticipated that a proportion of patients who are randomized to the CS arm will undergo AVR during the follow-up period. For endpoint analysis these patients remain in the CS arm.

11.4 General Statistical Considerations

Descriptive summaries will follow the conventions below.

- For continuous variables, summary statistics will include mean, standard deviation (or standard error for performance measurements), median, Q1, Q3, minimum, maximum, and sample size.
- For categorical (including ordinal) variables, summary statistics will include the count and percentage of subjects in each category.
- Time-to-event variable summaries will include the number of subjects at risk and Kaplan-Meier estimates at given time points. Standard errors will be calculated using Greenwood's formula.
- All measures will be tested at a significance level of 0.05 and/or 95% confidence interval will be presented, unless noted otherwise.
- No adjustment for multiplicity will be made on any endpoints other than the primary and secondary endpoints, unless noted otherwise.

11.5 Analysis of Primary and Secondary Endpoints

11.5.1 Primary Endpoint

The primary endpoint is a non-hierarchical composite of all-cause death, all stroke, and unplanned

cardiovascular hospitalization.

For the analysis of the primary endpoint, the trial arms will be compared using the log-rank test. The hypothesis for the primary endpoint is as follows:

$$H_0: S_C(t) = S_T(t)$$
$$H_a: S_C(t) \neq S_T(t)$$

where $S_C(t)$ represents the survival function for the control group at time t and $S_T(t)$ represents the survival function for the test group. A two-sided log-rank test will be performed using $\alpha=0.05$.

The analysis will be performed when the last patient reaches 2 years using all available data.

The primary endpoint will be evaluated on the ITT population.

In addition to the primary endpoint, the Kaplan-Meier (KM) rate for each arm through 2 years post-randomization and a 95% confidence interval will be presented for each of the individual components.

11.5.2 Center Poolability

Center poolability will be tested using a stratified log-rank test. The hypothesis for center poolability will be as follows:

$$H_0: \lambda_{jc}(t) = \lambda_{jT}(t) \quad \forall\ j=1, \ldots, k$$
$$H_a: \lambda_{jc}(t) = \varphi\lambda_{jT}(t) \quad \forall\ j=1, \ldots, k \text{ and } \varphi\neq 1$$

where the strata are the sites 1 through k and $\lambda_{jc}(t)$ represents the hazard for site j in the control arm at time t and $\lambda_{jT}(t)$ represents the hazard for site j in the test arm at time t. The center-poolability will be evaluated using stratified log-rank test at alpha level of 0.15. All available data at the time of analysis will be used. Once confirmed that there is no center effect, data from all centers will be combined for analysis.

11.5.3 Endpoints for Labeling

The labeling endpoints and their hypothesis tests are described in the sub-sections below. The order of presentation of these labeling endpoints is the order in which they will be tested.

11.5.3.1 Composite of Alive and KCCQ

A composite endpoint will be determined as follows at the 2-year post-randomization visit:

- Alive **and**
- KCCQ overall score of ≥75 **and**
- KCCQ did not decrease by more than 10 points compared to baseline

Patients will either considered to be a success (meet all of the above criteria) or a failure (fail at least one of the above criteria). In order to be a success all three criteria must be a success. If

any criterion is a failure then the subject is a failure regardless of the other measures. If one or more criteria are missing and all known criteria are a success then the subject will be set to missing since the success or failure cannot be determined.

The composite endpoint will be analyzed as with the following hypothesis.

$$H_0: R_{Test} = R_{Control}$$
$$H_A: R_{Test} \neq R_{Control}$$

where R_{Test} represents the success rate in the test arm and $R_{Control}$ represents the success rate in the control group. The hypothesis will be tested using a Fisher's exact test at the 0.05 level.

The composite endpoint will be tested on the ITT population.

In addition, the number and % of successes and the successes in each individual component will be presented for each trial arm.

11.5.3.2 Integrated Measure of LV Health

Integrated LV function will be determined as follows at the 2-year post-randomization visit:

- LV longitudinal global strain ≥ 15% **and**
- LV mass index < 115 g/m^2 for men or < 95 g/m^2 for women **and**
- LA volume index ≤ 34

Patients will either considered to be a success (meet all of the above criteria) or a failure (fail at least one of the above criteria). In order to be a success all three criteria must be a success. If any criterion is a failure then the subject is a failure regardless of the other measures. If one or more criteria are missing and all know criteria are a success then the subject will be set to missing since the success or failure cannot be determined.

Integrated LV function will be analyzed as with the following hypothesis.

$$H_0: R_{Test} = R_{Control}$$
$$H_A: R_{Test} \neq R_{Control}$$

where R_{Test} represents the success rate in the test arm and $R_{Control}$ represents the success rate in the control group. The hypothesis will be tested using a Fisher's exact test at the 0.05 level.

Integrated LV function will be tested on the ITT population.

In addition, the number and % of successes and the successes in each component will be presented for each trial arm.

11.5.3.3 Change in LVEF

The difference in the change in LVEF from baseline to 2-years post-randomization will be tested using a Wilcoxon Rank Sum Test. The following hypothesis will be tested:

$$H_0: D_{Test} \leq D_{Control}$$
$$H_A: D_{Test} > D_{Control}$$

where D_{Test} represents the difference in LVEF from baseline in the test group and $D_{Control}$ represents the difference in LVEF from baseline in the control group. This will be tested using a one-sided test with α=0.025 on the ITT population.

11.5.3.4 Additional Labeling Endpoints

The type I error for these endpoints will be controlled using the Hochberg method. These labeling endpoints and their hypothesis tests are described in the sub-sections below. The order of presentation of these labeling endpoints is irrelevant for application of the Hochberg method, and is not intended to create the appearance of a hierarchy.

11.5.3.5 New Onset Atrial Fibrillation

For the analysis of the new onset atrial fibrillation, the trial arms will be compared using the log-rank test. The hypothesis for the endpoint is as follows:

$$H_0: S_C(t) = S_T(t)$$
$$H_a: S_C(t) \neq S_T(t)$$

where $S_C(t)$ represents the survival function for the control group at time t and $S_T(t)$ represents the survival function for the test group. A two-sided log-rank test will be performed using α=0.05. All available data at the time of analysis will be used.

New onset atrial fibrillation will be evaluated on the ITT population.

In addition, the KM rate for each arm through 2-years post-randomization and a 95% confidence interval will be presented for new onset atrial fibrillation.

11.5.3.6 Death or disabling stroke

This endpoint will analyze the composite of death and/or disabling stroke. For this analysis, the trial arms will be compared using the log-rank test. The hypothesis for the endpoint is as follows:

$$H_0: S_C(t) = S_T(t)$$
$$H_A: S_C(t) \neq S_T(t)$$

where $S_C(t)$ represents the survival function for the control group at time t and $S_T(t)$ represents the survival function for the test group. A two-sided log-rank test will be performed using α=0.05. All available data at the time of analysis will be used.

Death and/or disabling stroke will be evaluated on the ITT population.

In addition, the KM rate for each arm through 2 years post-randomization and a 95% confidence interval will be presented for death or disabling stroke.

11.5.4 Controlling for Multiplicity

The endpoints in **Section 6.2** will be included in the labeling. A hierarchical gatekeeping approach

will be used to control the overall type I error between the primary endpoint and the endpoints for labeling. If the null hypothesis for the primary endpoint is rejected then the endpoints for labeling will be tested. If the primary endpoint's null hypothesis is not rejected, then none of the endpoints for labeling will be tested.

Within the endpoints for labeling, the family-wide type I error rate will be controlled at $\alpha=0.05$ using a mixture of hierarchical gatekeeping and the Hochberg method. If the null hypotheses are rejected for all the endpoints in **Sections 11.5.3.1** through **11.5.3.3,** then the hypotheses in **Section 11.5.3.4** will be tested and the overall Type I error rate controlled with the Hochberg method.

12 STUDY ADMINISTRATION

12.1 General Study Organization

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

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

As appropriate, Edwards Lifesciences will submit changes in the protocol to the FDA and Investigators for approval.

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

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

12.2 Data Safety Monitoring Board

A DSMB will monitor all AEs and SAEs to provide safety oversight. DSMB members will not be involved in the study and have no conflict of interest. DSMB activities, including stopping rules for early termination, will be defined in the DSMB Charter.

12.3 Clinical Events Committee

The CEC will adjudicate endpoint events and provide assessment of SAEs and device/procedure relatedness from enrollment through the primary endpoint. CEC activities will be defined in the CEC Charter.

12.4 Biomarker Assessment

Study patients will have blood collected for storage and assessment of cardiac biomarkers such as BNP at visits specified in **Section 8**. A core lab will be used for sample storage and standardized analysis. Samples will be stored frozen at the site and will be shipped to the core lab at regular, pre-specified intervals. Specific instructions and kits for sample collection, labeling and shipping will be provided to the sites.

12.5 Echocardiographic Core Lab

Study patients will receive an echocardiogram at the visits specified in **Section 8**. A central imaging core lab will be established to independently review and analyze echocardiographic images. A standardized protocol for acquiring images will be developed by the core lab and be provided to the clinical sites prior to study initiation. Sites will be trained on acquiring images prior to study initiation.

12.6 Computed Tomography Core Lab

All study patients will have a screening CT as referenced in **Section 8**. Sites will be trained on acquiring images prior to study initiation. In addition, all Screening CTs will be independently analyzed with regards to annular measurements by a CT/angiographic core lab.

12.7 Image Management

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

Instructions for image upload will be provided to investigative staff prior to study initiation. Investigative staff should upload all images to the image management core lab within 5 business days of data collection.

12.8 Histopathology

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

12.9 Training

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

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

Documentation of site personnel qualification and training should be maintained in the site's clinical trial files with copies provided to Edwards Lifesciences.

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

12.10 Data Management

Edwards Lifesciences will provide data management through a secure, password protected EDC system accessible via the Internet. A unique Patient ID will be assigned for each patient enrolled in the study. All pertinent data from the patient's records will be entered by the study site and core lab personnel into the eCRFs.

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

The site Principal Investigator or designee must ensure the accuracy and completeness of the recorded data and provide an 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.

12.11 Monitoring Procedures

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

12.12 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, Study Monitor, IRB/EC or appropriate regulatory authority.

In addition, Edwards has the right to limit or stop enrollment at a site. If this occurs, subjects enrolled prior to enrollment stop will continue to be followed per the protocol.

12.13 Auditing

The study may be subject to a quality assurance audit by Edwards Lifesciences or a designee, as well as inspection by appropriate regulatory authorities. It is important that the Investigator and relevant study personnel are available during any audits and that sufficient time is devoted to the process. In the event of an audit by regulatory authorities, the Investigator should contact Edwards Lifesciences as soon as possible.

12.14 Publication Policy

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

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.

13 ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Applicable Principles and Regulations

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

13.2 Institutional Review Board

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

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

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

13.3 Patient Informed Consent

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

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

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

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

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

13.4 Confidentiality

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

13.5 Investigator Records

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

- Clinical trial protocol and all amendments
- Signed Clinical Trial Agreement and any amendments
- IRB approval letters, including continuing reviews and all amendments/changes
- IRB approved informed consent documents
- All correspondence with another Investigator, IRB, Edwards Lifesciences, monitor or FDA, including required reports
- Records of receipt, use or disposition of a device

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

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

All clinical sites will maintain study records for a minimum of two years after marketing for this patient population approval is obtained or after the site is notified by Edwards Lifesciences that the study has been terminated. Record retention dates will be provided to all parties concerned by Edwards Lifesciences.

13.6 Investigator Reports

In addition to AE reporting requirements discussed in **Section 9.5**, the following reports are required:

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

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

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

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

13.7 Protocol Amendments

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

13.8 Protocol Deviations

An investigator must not make any changes or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency. Emergency changes do not require prior approval but must be reported to Edwards Lifesciences and the reviewing IRB within 5 days of the incident.

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

APPENDIX A ABBREVIATIONS

Abbreviation	Full Term
5MWT	5 Meter Walk Test
6MWT	Six-Minute Walk Test
ACC	American College of Cardiology
ACT	Activated Clotting Time
ADL	Activities of Daily Living
AE	Adverse Event
AHA	American Heart Association
ALT	Alanine Aminotransferase
AS	Aortic Stenosis
ASA	Aspirin
AST	Aspartate Aminotransferase
AVA	Aortic Valve Area
AVR	Aortic Valve Replacement
BMI	Body Mass Index
BMS	Bare Metal Stent
BNP	B-Type Natriuretic Peptide
CAD	Coronary Artery Disease
CCS	Canadian Cardiovascular Society
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
COVID-19	Coronavirus 2019
CRF	Case Report Form
CT	Computed Tomography
DES	Drug Eluting Stent
DoA	Delegation of Authority
DSMB	Data Safety Monitoring Board
EARLY TAVR	Evaluation of Transcatheter Aortic Valve Replacement Compared to SurveilLance for Patients with AsYmptomatic Severe Aortic Stenosis
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
EDC	Electronic Data Capture
EQ	EuroQol
FEV1	Forced Expiratory Volume in 1 Second
FDA	Food and Drug Administration
GCP	Good Clinical Practice
Hgb	Hemoglobin
ICF	Informed Consent Form

Abbreviation	Full Term
ICU	Intensive Care Unit
IDE	Investigational Device Exemption
IFU	Instructions for Use
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intent-to-treat
KCCQ	Kansas City Cardiomyopathy Questionnaire
LA	Left Atrial
LMW	Low Molecular Weight
LV	Left Ventricular
LVEF	Left Ventricular Ejection Fraction
MET	Metabolic Equivalent of Task
MR/MRI	Magnetic Resonance / Magnetic Resonance Imaging
mRS	Modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
NYHA	New York Heart Association
PA	Pulmonary Artery
PET	Polyethylene Terephthalate
PP	Per Protocol
PT	Prothrombin Time
PVL	Paravalvular Leak
QD	Every Day / Daily
QoL	Quality of Life
SAVR	Surgical Aortic Valve Replacement
SAE	Serious Adverse Event
STS	Society of Thoracic Surgeons
TAVR	Transcatheter Aortic Valve Replacement
TEE	Transesophageal Echocardiogram
THV	Transcatheter Heart Valve
TIA	Transient Ischemic Attack
TTE	Transthoracic Echocardiogram
UADE	Unanticipated Adverse Device Effect
UF	Unfractionated Heparin
VI	Valve Implant
WBC	White Blood Cell

APPENDIX B DEFINITIONS

<table>
<tr><th>Term</th><th>Definition</th><th>Reference/ Justification</th></tr>
<tr><td>6 Minute Walk Test</td><td>A performance-based measure of functional exercise capacity. The test measures the distance an individual is able to walk over a total of six minutes on a hard, flat surface. See more at: http://www.rheumatology.org/I-Am-A/Rheumatologist/Research/Clinician-Researchers/Six-Minute-Walk-Test-SMWT#sthash.cFCDWfkn.dpuf</td><td>ATS</td></tr>
<tr><td>Access Site</td><td>Any location (arterial or venous) traversed by a guidewire, a catheter or a sheath for TAVR</td><td>VARC-1</td></tr>
<tr><td>Access Site Related Complication</td><td>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.</td><td>VARC-1, VARC-2</td></tr>
<tr><td>Acute Kidney Injury (AKI)</td><td>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.</td><td>AKIN / KDIGO / VARC-2 / Sponsor</td></tr>
<tr><td>Adverse Event (AE)</td><td>Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device</td><td>ISO 14155-1:2011
GCP</td></tr>
<tr><td>Angina / Cardiac Chest Pain</td><td>Chest pain due to myocardial ischemia caused by an imbalance between myocardial blood supply and oxygen demand.</td><td>Sponsor</td></tr>
<tr><td>Angina, Grading Scale</td><td><table><tr><th>Grade</th><th>Description</th></tr><tr><td>I</td><td>Ordinary physical activity, such as walking and climbing stairs, does not cause angina. Angina occurs with strenuous, rapid, or prolonged exertion at work or during recreation</td></tr><tr><td>II</td><td>Slight limitation of ordinary activity. Angina occurs with walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, walking in the cold, into the wind, while under emotional stress, or during the first hours after awakening. Walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions, does not cause angina</td></tr><tr><td>III</td><td>Marked limitation of ordinary physical activity. Angina occurs with walking one to two blocks on the level and climbing one flight of stairs in normal conditions and at</td></tr></table></td><td>Canadian Cardiovascular Society</td></tr>
</table>

Term	Definition	Reference/ Justification
	a normal pace **IV** Inability to carry on any physical activity without discomfort. Angina syndrome may be present at rest	
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
Atrial Fibrillation	Atrial fibrillation is rapid irregular heart rhythm characterized by rapid and irregular beating of atria with or without associated ventricular fibrillation occurring for >24 hours and requiring treatment with rate/rhythm control drugs and/or anticoagulation and/or requiring chemical or electrical cardioversion. 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. • Long-standing persistent atrial fibrillation: Continuous atrial fibrillation >12 months in duration.	Sponsor
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 0: valve with no raphe Type 1: valve with one raphe Type 2: valve with two raphes	[64]
Bioprosthetic Valve Dysfunction (BVD)	Bioprosthetic valve dysfunction (BVD) can be either non-structural or structural: **Non-structural causes of BVD** (BVD due to extrinsic causes or processes unrelated to intrinsic function of valve leaflets) are	FDA

Term	Definition	Reference/ Justification
	defined as any of the following: • Paravalvular leak (PVL) • Endocarditis • Patient-prosthesis mismatch (PPM; moderate or severe per Valve Academic Research Consortium-2 (VARC 2) definitions) at discharge. **Structural BVD** should be defined as follows (regardless of whether or not findings drive therapy): • **Bioprosthetic valve hemodynamic dysfunction (BVHD)** ▪ Mild BVHD – A >50% increase in mean gradient from discharge, and/or new or progressive mild intra-prosthetic (i.e. central) aortic regurgitation (AR). If the mean gradient is greater than 20 or 40 mmHg, categorize as moderate or severe BVHD, respectively. ▪ Moderate BVHD – Mean gradient ≥20 mmHg, and/or new or progressive moderate intra-prosthetic AR ▪ Severe BVHD – Mean gradient ≥40 mmHg, and/or new or progressive severe intra-prosthetic AR • **Bioprosthetic valve structural deterioration (BVSD)** ▪ Anatomic imaging evaluation (echocardiography or CT) or autopsy findings demonstrate persistent bioprosthetic leaflet pathology related to i. structure (leaflet tears, etc.) ii. abnormal thickness without mobility change iii. mobility restriction (RLM) iv. calcification • **Bioprosthetic Valve Failure (BVF)** ▪ Referral for aortic valve re-intervention (valve-in-valve) or reoperation for progressive BVHD and/or BVSD ▪ Death from a cardiac cause ▪ An unexplained death following diagnosis of BVD in any of the above stages ▪ BVSD observed at autopsy likely related to cause of death	
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 **Procedural bleeding** has to be overt and actionable bleeding from vascular system either at or remote from the access/surgical site.	Sponsor

Term	Definition	Reference/ Justification
	Thresholds for reporting procedural bleeding for SAVR procedure is bloody chest tube output >600ml within any 24-hour period and for TF-TAVR >100 ml total EBL (Estimated Blood Loss) from access site. 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.	
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
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	STS

Term	Definition	Reference/ Justification
	• 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	
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
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 or SAVR procedure. Mechanical coronary artery obstruction following TAVR or index SAVR 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; OR • suture-related kinking or obstruction or cannulation- related obstruction of the coronary ostia associated with SAVR.	VARC-2/STS/ Sponsor
Device	For the determination of device relationship, the study device consists of: • The Edwards SAPIEN 3 valve • The Edwards SAPIEN 3 Ultra valve • The Edwards Valve Delivery System • The Edwards Expandable Sheath • Any surgical valve used implanted during index procedure	Sponsor
Device (Valve)	The separation of any portion of the frame into two or more parts;	Sponsor

Term	Definition	Reference/ Justification
Fracture	as may be determined by radiography, computed tomography, magnetic resonance imaging or by direct examination.	
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 or marketed.	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. Note that valve-associated thrombus identified at autopsy in a patient whose cause of death was not valve-related should not be reported as valve thrombosis	VARC-2
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, [80]
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
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	Any admission after study enrollment to an inpatient unit or hospital ward for ≥ 24h, including an emergency department stay. Hospitalizations planned for pre-existing conditions are excluded unless there is worsening of the baseline condition. Visits to urgent care centers or emergency departments < 24 hours may also be included if substantive intensification of therapy changes (e.g. heart failure episodes) are enacted (e.g. intravenous diuretics, significant increases in drug therapy dosages or addition of new pharmacotherapy agents). • Admission through ED or same day admission from a clinic will be considered an **unplanned** hospitalization • Admission for a pre-planned/ scheduled procedure or test will be considered a **planned** hospitalization.	VARC-3 / Sponsor
Hospitalization	Hospitalization for valve-related symptoms or worsening	

Term	Definition	Reference/ Justification
(Valve-related or Cardiovascular)	congestive heart failure includes: • hospitalizations for heart failure, angina, or syncope due to aortic valve disease requiring aortic valvuloplasty (BAV, AVR or Valve-in-valve) • hospitalization for clinical symptoms of CHF with objective signs AND administration of IV diuresis or inotropic therapy, institution of mechanical support (IABP or ventilation for pulmonary oedema) or haemodialysis for volume overload 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.	
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	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	NHLB (National Heart, Lung and Blood Institute)
Index Hospitalization (Index Procedure Hospitalization)	Index hospitalization is defined as the period of in hospital stay for the prosthetic valve implant (TAVR/SAVR) procedure for the TAVR arm subjects of the study. 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

<table>
<tr><th>Term</th><th>Definition</th><th>Reference/ Justification</th></tr>
<tr><td>LV Health</td><td>LV strain: ≥ 15%
LV mass index: ≤ 115 g/m^2 (men); < 95 (women)
LA volume index: ≤ 34</td><td>Sponsor</td></tr>
<tr><td>Liver Disease, Chronic</td><td>Any of the following:
MELD Score ≥10
Child-Pugh Class B or C, Portal-caval, spleno-renal, or transjugular intrahepatic portal shunt
Biopsy proven cirrhosis with portal hypertension or hepatocellular dysfunction
Child-Pugh Classification
The Child-Pugh score consists of five clinical features and is used to assess the prognosis of chronic liver disease and cirrhosis:
<table>
<tr><th>Measure</th><th>1 point</th><th>2 points</th><th>3 points</th></tr>
<tr><td>Total bilirubin, µmol/l (mg/dl)</td><td><34 (<2)</td><td>34-50 (2-3)</td><td>>50 (>3)</td></tr>
<tr><td>Serum albumin, g/dl</td><td>>3.5</td><td>2.8-3.5</td><td><2.8</td></tr>
<tr><td>PT, prolongation (secs)</td><td><4.0</td><td>4.0-6.0</td><td>>6.0</td></tr>
<tr><td>Ascites</td><td>None</td><td>Mild</td><td>Moderate to Severe</td></tr>
<tr><td>Hepatic encephalopathy</td><td>None</td><td>Grade I-II (or suppressed with medication)</td><td>Grade III-IV (or refractory)</td></tr>
</table>
Chronic liver disease is classified into Child-Pugh class A to C, employing the added score from above:
<table>
<tr><th>Points</th><th>Class</th><th>One-year survival</th><th>Two-year survival</th></tr>
<tr><td>5-6</td><td>A</td><td>100%</td><td>85%</td></tr>
<tr><td>7-9</td><td>B</td><td>81%</td><td>57%</td></tr>
<tr><td>10-15</td><td>C</td><td>45%</td><td>35%</td></tr>
</table></td><td>Sponsor/ VARC 2 [81]</td></tr>
<tr><td></td><td>MELD (Model for End-Stage Liver Disease) Score
A scoring system for assessing the severity and quantification of chronic liver disease.
• It is preferable to using the calculator (http://www.mdcalc.com/meld-score-model-for-end-stage-liver-disease-12-and-older/) to calculate the MELD as there are several caveats relating to minimum and maximum values assigned in the MELD
• Values should be no more than 48 hours old
In interpreting the MELD Score in hospitalized patients, the 3-month mortality is:
40 or more — 71.3% mortality
30–39 — 52.6% mortality
20–29 — 19.6% mortality
10–19 — 6.0% mortality
<9 — 1.9% mortality</td><td>[82]</td></tr>
</table>

Term	Definition	Reference/ Justification
Lung Disease, Severe	FEV1 <50% predicted or currently on home oxygen	Sponsor
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	[84]
Mortality, All-Cause	**Cardiovascular mortality** Any of the following criteria: • Death due to proximate cardiac cause (e.g. myocardial infarction, cardiac tamponade, worsening heart failure) • Death caused by non-coronary vascular conditions such as neurological events, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular disease • All procedure-related deaths, including those related to a complication of the procedure or treatment for a complication of the procedure • All valve-related deaths including structural or nonstructural valve dysfunction or other valve-related adverse events • Sudden or unwitnessed death • Death of unknown cause **Non-cardiovascular mortality** Any death in which the primary cause of death is clearly related to another condition (e.g. trauma, cancer, suicide).	VARC-2
Myocardial Infarction	An acute ischemic event that is associated with documented and clinically significant myocardial necrosis Any one of the following criteria meets the diagnosis for MI: **Periprocedural MI** (≤72H after Index procedure) New signs or symptoms of ischaemia. Symptoms like: • Chest pain or shortness of breath; • ECG changes indicative of new ischaemia (new ST segment elevation/depression of ≥1mm in ≥2 contiguous leads or new persistent left bundle branch block [LBBB]); • New pathological Q-waves in ≥2 contiguous leads; • Imaging evidence of a new loss of viable myocardium or new wall motion abnormality AND Elevated cardiac biomarkers (within 72 h of index procedure)	STS/VARC2

<table>
<tr><th>Term</th><th>Definition</th><th>Reference/ Justification</th></tr>
<tr><td></td><td>
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
Spontaneous MI (>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
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
</td><td></td></tr>
<tr><td>National Institutes of Health Stroke Scale (NIHSS)</td><td>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.</td><td>NIHSS/ Sponsor</td></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>85</td></tr>
<tr><td>Paravalvular Leak</td><td>Paravalvular or paraprosthetic leak (PVL) is a complication associated with the implantation of a prosthetic heart valve whether traditional (surgical) or a transcatheter (TAVR) approach.</td><td>ESC</td></tr>
</table>

Term	Definition	Reference/ Justification
	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	
Peripheral Vascular Disease (PVD)	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.	STS
Pulmonary Hypertension	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	ACC/Sponsor
Pre-existing Condition	A pre-existing condition is any chronic, recurring condition identified prior to enrollment in a clinical trial, whether present at enrollment or not. A preexisting condition is not an adverse event unless it worsens as a result of the study treatment.	Sponsor
Reintervention	Any intervention that repairs, alters or replaces a previously implanted or operated valve, which occurs after the completion of the valve implant procedure and the transfer to the procedure room. These interventions include: • Balloon aortic valvuloplasty • Surgical aortic valve replacement • Valve in valve • Paravalvular leak closure	STS/AATS

Serious Adverse Event (SAE)	Adverse Event that:
	• Leads to death;
	• Leads to a serious deterioration in the health of the study patient that:
	  ○ Results in life-threatening illness or injury;
	  ○ Results in a permanent impairment of a body structure or a body function;
	  ○ Requires inpatient hospitalization or prolongation of existing hospitalization;
		ISO 14155-1:2011
		FDA (21 CFR 312.32 (a)

Term	Definition	Reference/ Justification
	○ Results in medical or surgical intervention to prevent permanent impairment to body structure or a body function; • Led to fetal distress, fetal death or congenital abnormality or birth defect; • Significant medical event: Important medical events that do not meet the above criteria may still be considered an SAE if they seriously jeopardize the patient and require immediate medical or surgical intervention to prevent one of the aforementioned outcomes.	
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 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	VARC-2

Term	Definition	Reference/ Justification
	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 Modified Rankin score assessments should be made by qualified individuals according to a certification process	
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	[86]
STS Adult Cardiac Surgery Risk Calculator	The Society of Thoracic Surgeons' risk models predict the risk of operative mortality and morbidity after adult cardiac surgery on the basis of patient demographic and clinical variables. http://riskcalc.sts.org/stswebriskcalc/#/	STS
Syncope	A fainting spell or loss of consciousness	STS
SYNTAX Score	An angiographic grading tool to determine the complexity of coronary artery disease. http://www.syntaxscore.com/ http://ir-nwr.ru/calculators/syntaxscore/frameset.htm	
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)"	
Unanticipated Adverse Device Effect (UADE)	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problems associated with a device that relates to the rights, safety, or welfare of patients.	FDA
Valve Implant Procedure	Placement of study device and/or additional procedures occurring in the cath lab and/or operating room which are completed prior to subject transfer to a post-procedure recovery unit (e.g. Recovery Room, ICU/CCU, etc. The valve implant procedure will be considered to have started when the first interventional access related puncture (venous or arterial) is established for TAVR. The end of valve implant procedure is defined as date and time of vascular closure post eSheath removal (TAVR). Performance of TEE does not by itself constitute start of procedure	Sponsor
Valve	**Valve migration**	VARC-2

Term	Definition	Reference/ Justification
Malpositioning	• 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	
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

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