# ExCEED:

A Prospective, Single-arm, Controlled, Multicenter Study to **E**stablish the Safety and Effectiveness of the **CE**NTERA THV System in Interm**ED**iate Risk Patients who have Symptomatic, Severe, Calcific, Aortic Stenosis Requiring Aortic Valve Replacement

**NCT03517436**

**July 29, 2021**

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**Clinical Protocol**
**Study Number: 2017-18**
Version 2.0
July 29, 2021

**Study Sponsor:**
Edwards Lifesciences LLC
One Edwards Way
Irvine, CA 92614
USA

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## PROTOCOL SYNOPSIS

| | |
|---|---|
| **Title** | A Prospective, Single-arm, Controlled, Multicenter Study to **E**stablish the Safety and Effectiveness of the **CE**NTERA THV System in Interm**ED**iate Risk Patients who have Symptomatic, Severe, Calcific, Aortic Stenosis Requiring Aortic Valve Replacement (ExCEED) |
| **Objective** | Following discontinuation of the CENTERA program, the objective is to monitor the safety and valve performance of the Edwards CENTERA Transcatheter Heart Valve (THV) System in patients with symptomatic, severe, calcific aortic stenosis who are at intermediate operative risk for surgical aortic valve replacement (SAVR) |
| **Study Device** | Edwards CENTERA THV System |
| **Control** | NA |
| **Study Design** | Prospective, single-arm, multicenter study. |
| **Study Population** | Subjects with symptomatic, severe, calcific AS and appropriate iliofemoral anatomy who are at intermediate operative risk |
| **Sample Size** | A sample size of 750 subjects was planned; 101 subjects were enrolled at the time of enrollment closure. Up to two roll-in subjects were allowed per site; roll-in subjects were not counted towards the enrolled sample size. |
| **Study Sites** | Up to 65 actively enrolling sites in the US was planned; 23 US sites enrolled subjects at the time of enrollment closure. |
| **Visit Schedule** | Office Visit: Screening, Procedure, Post-Procedure, Discharge, 30 days, Years 1-5, 7 and 10<br>Phone: Years 6, 8, 9 |
| **Study Outcomes** | The following outcomes will be evaluated:<br>1. Mortality at 30 days, 1 year and annually (up to 10 years)<br>2. Stroke at 30 days, 1 year and annually (up to 10 years)<br>3. Aortic valve reintervention at 30 days, 1 year and annually (up to 10 years)<br>4. Structural valve deterioration at years 1-5, 7 and 10<br>5. Hemodynamic valve performance evaluation by echocardiography including AV stenosis and AV regurgitation (paravalvular & central) at 30 days, and years 1-5, 7 and 10 |
| **Inclusion Criteria** | Candidates must meet all of the following criteria to be included in the study:<br>1. Severe, calcific AS meeting the following transthoracic echocardiogram (TTE) criteria:<br>• AV area ≤ 1.0 $cm^2$ OR AV area index ≤ 0.6 $cm^2/m^2$<br>• Jet velocity ≥ 4.0 m/s OR mean gradient ≥ 40 mmHg |

2. NYHA functional class ≥ II
3. Judged by the Heart Team to be at intermediate risk for open surgical therapy (i.e., predicted risk of surgical mortality ≥ 3% and < 8% at 30 days, based on the Society of Thoracic Surgeons (STS) risk score and other clinical co-morbidities unmeasured by the risk calculator)
4. The subject has been informed of the nature of the study, agrees to its provisions and has provided written informed consent as approved by the Institutional Review Board/Ethics Committee of the respective clinical site.

**Exclusion Criteria**

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

1. Native aortic annulus size unsuitable for sizes 23, 26 or 29 mm CENTERA THV based on 3D imaging analysis
2. Aortic valve is unicuspid, bicuspid or non-calcified
3. Pre-existing mechanical or bioprosthetic valve in any position. (Of note, mitral ring is not an exclusion).
4. Known hypersensitivity to Nitinol (nickel or titanium)
5. Severe aortic regurgitation (> 3+)
6. Severe mitral regurgitation (> 3+) or ≥ moderate stenosis
7. Ventricular dysfunction with left ventricular ejection fraction (LVEF) < 30%
8. Cardiac imaging (echocardiography, computed tomography and/or magnetic resonance imaging) evidence of intracardiac mass, thrombus or vegetation
9. Evidence of an acute myocardial infarction ≤ 30 days before the valve implant procedure
10. Subjects with planned concomitant ablation for atrial fibrillation
11. Hypertrophic cardiomyopathy with obstruction (HOCM)
12. Coronary anatomy that increases the risk of coronary artery obstruction post-TAVR
13. Complex coronary artery disease (CAD):
    a. Unprotected left main coronary artery
    b. SYNTAX score > 32 (in the absence of prior revascularization)
    c. Heart Team assessment that optimal revascularization cannot be performed
14. Iliofemoral vessel characteristics that would preclude safe placement of the introducer sheath.
15. Significant abdominal or thoracic aortic disease that would preclude safe passage of the delivery system

16. Active bacterial endocarditis within 180 days of the valve implant procedure
17. Stroke or transient ischemic attack within 90 days of the valve implant procedure
18. Symptomatic carotid or vertebral artery disease or successful treatment of carotid stenosis within 30 days of the valve implant procedure
19. Severe lung disease (Forced Ejection Volume 1 (FEV1) < 50% predicted) or currently on home oxygen
20. Severe pulmonary hypertension (e.g., pulmonary artery systolic pressure ≥ 2/3 systemic pressure)
21. Hemodynamic or respiratory instability requiring inotropic support, mechanical ventilation or mechanical heart assistance within 30 days of the valve implant procedure
22. History of cirrhosis or any active liver disease
23. Renal insufficiency (estimated glomerular filtration rate (eGFR) < 30 mL/min per the Cockcroft-Gault formula) and/or renal replacement therapy at the time of screening
24. 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
25. Inability to tolerate or condition precluding treatment with antithrombotic therapy during or after the valve implant procedure
26. Absolute contraindications or allergy to iodinated contrast that cannot be adequately treated with pre-medication
27. Significant frailty as determined by the Heart Team (after objective assessment of frailty parameters)
28. Immobility that would prevent completion of study procedures (e.g., six-minute walk tests, etc.)
29. Subject refuses blood products
30. Body mass index > 50 kg/$m^2$
31. Estimated life expectancy < 24 months
32. Positive urine or serum pregnancy test in female subjects of childbearing potential
33. Currently participating in an investigational drug or another device study. Note: Trials requiring extended follow-up for products that were investigational, but have since become commercially available, are not considered investigational trials. Observational studies are not considered exclusionary.

| | |
|---|---|
| **Statistical Methods** | Summary data for the 101 enrolled patients will be presented with descriptive statistics; no hypothesis testing will be performed. |

| | |
|---|---|
| **Principal Investigators** | Martin Leon, MD, FACC<br>Columbia University Medical Center/ NY Presbyterian Hospital<br>New York, NY |
| **Sponsor** | Edwards Lifesciences LLC<br>One Edwards Way<br>Irvine, CA 92614 |

**INVESTIGATOR SIGNATURE PAGE**

Protocol Title: ExCEED: A Prospective, Single-arm, Controlled, Multicenter Study to Establish the Safety and Effectiveness of the CENTERA THV System in IntermEDiate Risk Patients who have Symptomatic, Severe, Calcific, Aortic Stenosis Requiring Aortic Valve Replacement

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

_____

Investigative Site Name

_____

Site Principal Investigator Name (print)

_____ _____

Site Principal Investigator Signature Date

# 1 INTRODUCTION

## 1.1 Aortic Stenosis

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

Bicuspid aortic valve morphology is a common congenital valvular abnormality, occurring in 0.5% to 2% of the general population.[4] AS is also a frequent complication in this population and may occur at a younger age in patients with a bicuspid valve, when compared with patients with a tricuspid aortic valve morphology.[5,6]

## 1.2 Treatment of AS

Relief of aortic valve obstruction typically results in an improvement of symptoms, hemodynamic parameters, and global left ventricle systolic function, as well as reversal of left ventricular hypertrophy.[7,8] Treatment options for patients with severe, symptomatic AS include medical management, percutaneous balloon aortic valvuloplasty (BAV) or aortic valve replacement (AVR).

AVR is considered the gold standard for treatment of patients with severe, symptomatic AS [9]. AVR may be performed surgically or percutaneously. Outcomes after surgical AVR (SAVR) are excellent in patients who do not have a high procedural risk, resulting in an improvement in symptoms, and in most patients, an improvement in exercise tolerance.[10-14]

Transcatheter aortic valve replacement (TAVR) was originally developed as an alternative to SAVR in patients who were at high risk for surgical mortality or who were not suitable for surgical intervention, with the first successful TAVR procedure performed by Cribier and colleagues in 2002.[15]

The Placement of AoRtic TranNscathetER valve (PARTNER) study, Cohort B compared standard medical therapy (including BAV) to TAVR in patients with severe AS who were not candidates for surgical intervention. Mortality rates at 1 year were significantly lower in the TAVR cohort compared to those who underwent medical therapy (30.7% vs. 50.7%, $p<0.001$).[16] At 5-years, 71.8% of TAVR patients had died compared to 93.6% of patients treated medically ($p<0.0001$).[17]

In another study evaluating treatment of patients not suitable for surgery, self-expanding valves also showed superiority to medical therapy. Comparing to an objective performance goal (OPG)

derived from the medical therapy arm of the PARTNER 1 Cohort B study, the rate of all-cause mortality or major stroke at 12 months was 26.0% with self-expanding TAVR versus 43.0% with the medical therapy OPG ($p < 0.0001$).[18]

Two broad categories of devices for TAVR include balloon-expandable valves and self-expanding valves. The Edwards SAPIEN transcatheter heart valve (THV), the first-generation balloon-expandable valve, consists of a trileaflet, bovine pericardial tissue valve attached to a stainless-steel frame; this valve has been commercially available in the US since November 2011. Newer generations of balloon-expandable valves include the Edwards SAPIEN XT THV and the Edwards SAPIEN 3 THV, which have cobalt chromium frames.

Self-expanding valves have the advantage of being able to be recaptured and repositioned prior to detachment. The first self-expanding THV, the Medtronic CoreValve System (Medtronic Inc., Minneapolis, MN), obtained Food and Drug Administration (FDA) approval in January 2014. The CoreValve consists of self-expanding trileaflet porcine pericardial tissue with a Nitinol frame. This was followed by the Medtronic CoreValve Evolut R valve and later by the newest-generation Evolut Pro valve. A number of other self-expanding THVs are available outside the US.

Although patients with bicuspid valve morphology have historically been excluded from TAVR studies, recent reports indicate the use of transcatheter heart valves in these patients is feasible and effective with favorable valve performance.[19-23]

### 1.2.1 TAVR vs. SAVR

Numerous studies have been performed comparing TAVR to SAVR. Studies comparing the two treatments in patients at high surgical risk have shown superiority of TAVR to SAVR with both balloon-expandable and self-expanding valves:

- In the PARTNER study using the balloon-expandable SAPIEN THV, 1-year mortality rates were reported to be 24.2% vs. 26.8% ($p = 0.001$ for noninferiority) for TAVR and SAVR, respectively. During 5-year follow-up, mortality rates were similar between the TAVR and SAVR (67.8% vs. 62.4%, $p=0.76$). There was also no statistical difference between the two groups in the rate of stroke, repeat hospitalization or the need for a new pacemaker at one year, however peri-procedural risks at 30 days differed with statistically significant higher risk of major bleeding and new-onset atrial fibrillation with SAVR and higher incidence of vascular complications with TAVR.[24]
- In a randomized study of patients using the self-expanding CoreValve, the rate of all cause-death at 1 year was significantly lower in the TAVR group than in the surgical group (14.2% vs. 19.1%), with an absolute reduction in risk of 4.9 percentage points ($P<0.001$ for noninferiority; $P = 0.04$ for superiority). The rate of major adverse cardiovascular and cerebrovascular events (MACCE) at 1 year was significantly lower in the TAVR group than in the SAVR group (20.4% vs. 27.3%, $P = 0.03$). Major vascular complications and permanent pacemaker implantations were significantly more frequent in the TAVR group than in SAVR, whereas bleeding, acute kidney injury (AKI), and new-onset atrial fibrillation were significantly more common in the SAVR group than in the TAVR group.[25]

- Similar results were found in a large 4659 patients meta-analysis, which showed that TAVR had similar cardiovascular and all-cause mortality to SAVR at early and long-term follow-up. There was no significant difference in the incidence of myocardial infarction (MI) (p = 0.59), stroke (p = 0.36), and transient ischemic attack (TIA) (p = 0.85) at averages of 72, 66, and 89 weeks, respectively. TAVR was superior to SAVR for major bleeding complications and noninferior to SAVR for MACCE.[26]

In patients with intermediate surgical risk, TAVR has been shown to be at least non-inferior to SAVR:

- In trials evaluating balloon-expandable valves, there was no difference between TAVR and SAVR for the primary endpoint of all-cause death or disabling stroke at 2 years (Hazard Ratio: 0.89; 95% CI: 0.73 to 1.09; p=0.25). All-cause mortality occurred in 16.7% of those randomized to TAVR with SAPIEN XT, compared with 18.0% of those treated with SAVR. Disabling stroke occurred in 6.2% of patients treated with TAVR and 6.3% of patients treated with SAVR[27] In a propensity score-matched comparison of the SAPIEN 3 TAVR patients and PARTNER II Cohort A SAVR patients, TAVR was both noninferior and superior to SAVR (propensity score pooled weighted proportion difference: –9.2%; 95% Confidence Interval (CI): –13.0 to –5.4; p<0.0001). At 1 year, the rate of all-cause death was 7.4%, disabling stroke occurred in 2%, reintervention was required in 1%, and moderate or severe paravalvular leak (PVL) was seen in 2%[28]
- A randomized study comparing TAVR with the self-expanding CoreValve to SAVR showed TAVR to be non-inferior alternative to SAVR. At 24 months, the estimated incidence of the primary endpoint composite of all-cause death and disabling stroke was 12.6% in the TAVR group and 14.0% in the surgery group (95% credible interval [Bayesian analysis] for difference, −5.2 to 2.3%; posterior probability of noninferiority, >0.999).[29]

As a result of these findings, the American College of Cardiology (ACC)/American Heart Association (AHA) guideline committees have provided TAVR with a Class I and IIa recommendation for patients with severe AS with high/prohibitive and intermediate surgical risk, respectively.[30] And according to the 2017 European Society of Cardiology (ESC)/ European Association for Cardio-Thoracic Surgery (EACTS) guidelines on valvular heart diseases, TAVR is favored over SAVR in elderly patients with suitable transfemoral access and elevated surgical risk.[31]

### 1.3 CENTERA THV Clinical History

The following section presents the results of 3 clinical studies sponsored by Edwards Lifesciences. These studies reported the incidence of mortality, adverse events and a summary of device efficacy including hemodynamic valve performance and functional improvement in implanted patients.

The CENTERA THV System received CE Mark approval in February 2018. Edwards discontinued the CENTERA program in July 2019; the CENTERA THV System is no longer commercially available.

### 1.3.1 CENTERA Study #2014-03

The CENTERA THV clinical study (#2014-03) was a non-randomized, prospective, multi-center safety and device success study. A total of 247 patients deemed at high risk for surgical intervention were enrolled in the CENTERA trial at 26 participating sites from March 12, 2015 through June 28, 2016.

Treatment was initiated in 203 patients (As Treated Population). Primary and secondary endpoints were evaluated for the As Treated population. A CENTERA THV (Model 9550C) was implanted in 198 patients (Valve Implant Population). However, the CENTERA THV was explanted in one patient on the same day as the implant procedure due to coronary artery obstruction. Hemodynamic and echocardiographic assessments were performed in 197 patients.

Patients were assessed at the following intervals: baseline, hospital discharge, 30 days, 6 months and 1 year and will be followed annually thereafter through 5 years.

#### 1.3.1.1 Demographics and Baseline Characteristics

Mean age at enrollment in the As Treated population (AT Population, N=203) was 82.7 ± 5.5 years, and ranged from 60 to 94 years. The majority of patients were female (67.5%). Mean STS score was 6.1% ± 4.2% and there were 138/203 patients in New York Heart Association (NYHA) functional Class III/IV (68.0%). Demographics and baseline characteristics are presented in **Table 1**.

**Table 1: CENTERA Study #2014-03: Demographics and Baseline Characteristics**

| Baseline Characteristic | Summary Statistic | As Treated Population (N=203) | Valve Implant Population (N=198) |
|---|---|---|---|
| Age (Years) | n | 203 | 198 |
| | Mean | 82.7 | 82.8 |
| | Std | 5.51 | 5.42 |
| | Median | 84.0 | 84.0 |
| | Min | 60.0 | 60.0 |
| | Max | 94.0 | 94.0 |
| Sex | | | |
| Female | n / N (%) | 137/203 (67.5%) | 136/198 (68.7%) |
| Male | n / N (%) | 66/203 (32.5%) | 62/198 (31.3%) |
| Height (cm) | n | 203 | 198 |
| | Mean | 163.6 | 163.5 |
| | Std | 8.75 | 8.60 |
| | Median | 163.0 | 162.5 |
| | Min | 145.0 | 145.0 |
| | Max | 188.0 | 188.0 |
| Weight (kg) | n | 203 | 198 |
| | Mean | 71.8 | 71.7 |

**Table 1: CENTERA Study #2014-03: Demographics and Baseline Characteristics**

| Baseline Characteristic | Summary Statistic | As Treated Population (N=203) | Valve Implant Population (N=198) |
|---|---|---|---|
| | Std | 16.52 | 16.01 |
| | Median | 71.0 | 70.7 |
| | Min | 40.0 | 40.0 |
| | Max | 153.2 | 153.2 |
| Body Mass Index (kg/m$^2$) | n | 203 | 198 |
| | Mean | 26.8 | 26.8 |
| | Std | 5.36 | 5.33 |
| | Median | 26.0 | 26.0 |
| | Min | 14.3 | 14.3 |
| | Max | 44.8 | 44.8 |
| Body Surface Area (m$^2$) | n | 203 | 198 |
| | Mean | 1.8 | 1.8 |
| | Std | 0.21 | 0.21 |
| | Median | 1.8 | 1.8 |
| | Min | 1.3 | 1.3 |
| | Max | 2.7 | 2.7 |
| **RISK SCORES** | | | |
| STS Score | n | 203 | 198 |
| | Mean | 6.1 | 6.2 |
| | Std | 4.19 | 4.22 |
| | Median | 5.0 | 5.1 |
| | Min | 1.4 | 1.5 |
| | Max | 28.0 | 28.0 |
| Logistic EuroSCORE 1 | n | 203 | 198 |
| | Mean | 17.1 | 17.1 |
| | Std | 9.84 | 9.92 |
| | Median | 15.2 | 15.2 |
| | Min | 3.6 | 3.6 |
| | Max | 84.0 | 84.0 |
| EuroSCORE 2 | n | 202 | 198 |
| | Mean | 5.1 | 5.1 |
| | Std | 3.95 | 3.96 |
| | Median | 3.8 | 3.8 |
| | Min | 0.8 | 0.8 |
| | Max | 27.2 | 27.2 |
| NYHA Class | | | |
| Class I | n / N (%) | 1/203 (0.5%) | 1/198 (0.5%) |

**Table 1: CENTERA Study #2014-03: Demographics and Baseline Characteristics**

| Baseline Characteristic | Summary Statistic | As Treated Population (N=203) | Valve Implant Population (N=198) |
|---|---|---|---|
| Class II | n / N (%) | 64/203 (31.5%) | 62/198 (31.3%) |
| Class III | n / N (%) | 126/203 (62.1%) | 124/198 (62.6%) |
| Class IV | n / N (%) | 12/203 (5.9%) | 11/198 (5.6%) |
| NYHA Class Grouped | | | |
| Class I/II | n / N (%) | 65/203 (32.0%) | 63/198 (31.8%) |
| Class III/IV | n / N (%) | 138/203 (68.0%) | 135/198 (68.2%) |
| Source: Table 1.3 based on data extracted 18JAN2018 and run on 19JAN2018 | | | |

#### 1.3.1.2 Procedural Information

The CENTERA THV was implanted via transfemoral access in 198 of 203 patients (97.5%). A size 26 mm valve was implanted in 117 patients (59.1%), a size 29 mm valve was implanted in 59 patients (29.8%), and a size 23 mm valve was implanted in 22 patients (11.1%). The CENTERA THV was recaptured and repositioned in 7 patients (3.4%) with no ventricular or aortic injury. There were no ectopic valve deployments.

#### 1.3.1.3 Primary Endpoint: 30-Day All-Cause Mortality

Two patients died within 30 days after the index procedure. The Kaplan-Meier (KM) estimate for all-cause mortality at 30-days was 0.99%. The primary endpoint was met as this rate is lower than the study hypothesis of <10% mortality at 30-days post-index procedure. A summary of all-cause mortality is presented in **Table 2**.

**Table 2: CENTERA Study #2014-03: Primary Endpoint: 30-Day All-Cause Mortality (AT Population, N=203)**

| Event | KM Rate* | SE of KM | 90% CI | No. of Events | No. of Pts with Events | No. of Pts at Risk | P-Value† |
|---|---|---|---|---|---|---|---|
| All-Cause Mortality | 0.0099 | 0.0069 | (0.0031, 0.0312) | 2 | 2 | 199 | <.0001 |

Source: Table 2.1 based on data extracted 18JAN2018 and run on 19JAN2018
Note: Imputed dates are used for events with missing or incomplete onset dates.
* Kaplan-Meier estimates are through 30 days. Events occurring after 30 days are not included in this analysis.
† P-value is from one-sided test on a null hypothesis that the event rate was ≥10%.

#### 1.3.1.4 Secondary Endpoint: Device Success at 30 Days

Overall device success was reported in 131 of 138 patients (94.9%). A summary of device success is presented in **Table 3**.

**Table 3: CENTERA Study #2014-03: Device Success at 30 Days (AT Population, N=203)**

| Factor | Result |
|---|---|
| Overall Device Success* | 131/138 (94.9%) |
| Factor 1: Alive at 3 Days (CEC) | 201/203 (99.0%) |
| Factor 2: Single device in proper position | 160/165 (97.0%) |
| Factor 3: Intended Performance of the CENTERA valve at 30 Days (echo core lab) | 159/161 (98.8%) |

Source: Table 3.1.1 based on data extracted 18JAN2018 and run on 19JAN2018
Note: Summary statistics: Categorical measures – n/N (%)
* Device success is defined as a composite of the following events:
Factor 1: Absence of procedural mortality
Factor 2: Correct positioning of a single prosthetic valve into the proper anatomical location
Factor 3: Intended performance of the prosthetic heart valve (per the 30 day core lab echo assessment).
The intended performance is defined as
- Total AR of none/trace/mild/mild-moderate and
- At least one of the following is true:
  - Patient prosthesis mismatch of insignificant and mean gradient < 20 mmHg or
  - Patient prosthesis mismatch of insignificant and peak velocity < 3 m/s or
  - Mean Gradient < 20 mmHg and peak velocity < 3m/s

#### 1.3.1.5 CEC-Adjudicated Adverse Events

Through 1 year of follow-up, there were a total of 18 deaths corresponding to a KM estimate of 9.1% for all-cause mortality. Nine deaths were adjudicated as cardiovascular-related deaths. Twenty-two cerebrovascular events were reported in 20 patients including 6 instances of TIA in 5 patients and 16 stroke events in 15 patients, 8 of which were disabling stroke. Through 1 year, new onset conduction abnormalities requiring pacemaker implantation was reported in 11 patients (KM estimate: 5.5%). Clinical Events Committee (CEC)-adjudicated adverse events (AEs) are presented in Table 4.

**Table 4: CENTERA Study #2014-03: CEC-Adjudicated AEs through 1 Year (KM) (AT Population, N=203)**

| Event | 30 Days | 180 Days | 1 Year* |
|---|---|---|---|
| Death | 1.0% (2,2) | 5.0% (10,10) | 9.1% (18,18) |
| Cardiovascular Death | 1.0% (2,2) | 2.0% (4,4) | 4.6% (9,9) |
| Non-Cardiovascular Death | 0.0% (0,0) | 3.0% (6,6) | 4.7% (9,9) |
| Myocardial Infarction | 1.5% (3,3) | 1.5% (3,3) | 2.0% (4,4) |
| Periprocedural MI (Beginning ≤ 72 hours of Index procedure) | 1.0% (2,2) | 1.0% (2,2) | 1.0% (2,2) |
| Spontaneous MI | 0.5% (1,1) | 0.5% (1,1) | 1.0% (2,2) |
| Cerebrovascular Event | 5.0% (10,10) | 7.5% (15,15) | 10.2% (22,20) |
| TIA | 1.0% (2,2) | 1.5% (3,3) | 2.6% (6,5) |

**Table 4: CENTERA Study #2014-03: CEC-Adjudicated AEs through 1 Year (KM) (AT Population, N=203)**

| Event | 30 Days | 180 Days | 1 Year* |
|---|---|---|---|
| Stroke (Any) | 4.0% (8,8) | 6.0% (12,12) | 7.6% (16,15) |
| Disabling Stroke | 2.5% (5,5) | 3.0% (6,6) | 4.1% (8,8) |
| Non-Disabling Stroke | 1.5% (3,3) | 3.0% (6,6) | 4.1% (8,8) |
| Other Cerebrovascular Event | 0.0% (0,0) | 0.0% (0,0) | 0.0% (0,0) |
| Bleeding‡ | 18.2% (40,37) | NA | NA |
| Life-Threatening or Disabling Bleeding‡ | 4.9% (10,10) | NA | NA |
| Major Bleeding‡ | 14.4% (30,29) | NA | NA |
| Vascular Access Site and Access-related complications‡ | 6.4% (14,13) | NA | NA |
| Major Vascular Complication‡ | 6.4% (14,13) | NA | NA |
| Percutaneous closure device failure‡ | 0.5% (1,1) | NA | NA |
| Acute Kidney Injury† | 3.5% (7,7) | NA | NA |
| Stage I AKI† | 2.5% (5,5) | NA | NA |
| Stage II AKI† | 0.5% (1,1) | NA | NA |
| Stage III AKI† | 0.5% (1,1) | NA | NA |
| New Conduction Abnormality | 24.7% (53,50) | 28.3% (60,57) | 29.4% (62,59) |
| Atrial Fibrillation | 8.0% (16,16) | 11.0% (22,22) | 11.6% (23,23) |
| New Conduction Abnormality Requiring a Pacemaker | 4.9% (11,10) | 4.9% (11,10) | 5.5% (12,11) |
| Prosthetic valve endocarditis | 0.0% (0,0) | 0.5% (1,1) | 0.5% (1,1) |
| Prosthetic valve thrombosis | 0.0% (0,0) | 0.5% (1,1) | 1.0% (2,2) |
| Valve embolization | 0.5% (1,1) | 0.5% (1,1) | 0.5% (1,1) |
| Valve migration | 0.0% (0,0) | 0.0% (0,0) | 0.0% (0,0) |
| Coronary artery obstruction requiring intervention‡ | 0.5% (1,1) | NA | NA |
| Rehospitalization for valve related symptoms of CHF or worsening CHF | 0.5% (1,1) | 3.6% (8,7) | 6.8% (18,13) |

Source: Table 5.3.1.1 based on data extracted 18JAN2018 and run on 04FEB2018
Note: Kaplan-Meier estimate - % (no. events, no. of subjects with the event)
Imputed dates are used for events with incomplete onset dates
* 1 Year is determined as 365 days.
† Adjudicated only up to 7 days
‡ Adjudicated only up to 30 days

#### 1.3.1.6 Patient Prosthesis Mismatch

Patient prosthesis mismatch (PPM) was evaluated at discharge, 30 days, 6 months and 1 year. Among 129 patients evaluated at 1-year follow-up, moderate PPM was observed in 21 patients (16.3%) and severe PPM in 7 patients (5.4%). A summary of PPM through 1 year is presented in **Table 5**.

**Table 5: CENTERA Study #2014-03: Patient Prosthesis Mismatch through 1 Year (VI Population*, N=197)**

| | Insignificant | Moderate | Severe |
|---|---|---|---|
| Discharge | 122/143 (85.3%) | 16/143 (11.2%) | 5/143 (3.5%) |
| 30 Days | 126/145 (86.9%) | 11/145 (7.6%) | 8/145 (5.5%) |
| 6 Months | 110/136 (80.9%) | 22/136 (16.2%) | 4/136 (2.9%) |
| 1 Year | 101/129 (78.3%) | 21/129 (16.3%) | 7/129 (5.4%) |

Source: Table 3.3.3.3 based on data extracted 18JAN2018 and run on 26JAN2018
Note: Summary statistics:
Categorical measures-No. / Total no. (%)
Insignificant PPM is an EOAi > 0.85 $cm^2/m^2$ for patients with a BMI < 30 and EOAi > 0.70 $cm^2/m^2$ for patients with BMI ≥ 30
Moderate PPM is an EOAi of 0.65-0.85 $cm^2/m^2$ for patients with a BMI < 30 and EOAi of 0.60-0.70 $cm^2/m^2$ for patients with BMI ≥ 30
Severe PPM is an EOAi of <0.65 $cm^2/m^2$ for patients with a BMI < 30 and EOAi of <0.60 $cm^2/m^2$ for patients with BMI ≥ 30
* Subject CNT 0354 014 was removed from VI population for this analysis due explant on the same day as implant procedure

#### 1.3.1.7 Structural Valve Deterioration Requiring Reintervention

There have been no instances of structural valve deterioration (SVD) requiring reintervention reported for this study.

#### 1.3.1.8 Prosthetic Valve Dysfunction through 1 Year

At 1-year follow-up, valve dysfunction was reported in 2 of 129 patients evaluated (1.6%). A summary of prosthetic valve dysfunction is presented in **Table 6**.

**Table 6: CENTERA Study #2014-03: Prosthetic Valve Dysfunction through 1 Year (VI Population*, N=197)**

| | Discharge | 30 Days | 6 Months | 1 Year |
|---|---|---|---|---|
| Prosthetic Valve Dysfunction | 2/160 (1.3%) | 3/151 (2.0%) | 3/142 (2.1%) | 2/129 (1.6%) |
| 95% Exact CI | (0.15%, 4.44%) | (0.41%, 5.70%) | (0.44%, 6.05%) | (0.19%, 5.49%) |

Source: Table 3.3.6.0 based on data extracted 18JAN2018 and run on 25JAN2018
Note: Summary statistics: Categorical measures – n/N (%)
* Subject CNT 0354 014 was removed from VI population for this analysis due explant on the same day as implant procedure
A subject is considered to have prosthetic valve dysfunction if
- They have total aortic regurgitation or Moderate/Moderate-Severe/Severe or
- If the mean gradient ≥ 20 mmHg and EOA ≤ 1.1 for BSA ≥ 1.6; EOA ≤ 0.9 for BSA<1.6 or
- If the mean gradient ≥ 20 mmHg and DVI ≤ 0.35 or
- If EOA ≤ 1.1 for BSA ≥ 1.6; EOA ≤ 0.9 for BSA<1.6 and DVI ≤ 0.35

#### 1.3.1.9 Effectiveness Endpoints

Hemodynamic and functional assessments demonstrated favorable clinical outcomes and valve performance in patients implanted with the CENTERA THV (**Table 7**). Significant improvement from baseline in NYHA functional class and Six-Minute Walk Test (6MWT) evaluation was observed through 1 year of follow-up (p<0.0001 and p=0.0067, respectively). Echocardiographic Core Lab evaluation demonstrated sustained significant reduction in mean transvalvular gradients from baseline through 1-year follow-up (p<0.0001). Additionally, significant improvements in effective orifice area (EOA) and index orifice area from baseline through 1 year were reported (p<0.0001).

**Table 7: CENTERA Study #2014-03: Effectiveness Endpoints through 1 Year (VI Population*, N=197)**

| | | Baseline | Discharge | 30 Days | 6 Months | 1 Year |
|---|---|---|---|---|---|---|
| NYHA Class | I | 1 /197 (0.5%) | 76 /187 (40.6%) | 98 /185 (53.0%) | 82 /176 (46.6%) | 82 /171 (48.0%) |
| | II | 62 /197 (31.5%) | 90 /187 (48.1%) | 74 /185 (40.0%) | 77 /176 (43.8%) | 74 /171 (43.3%) |
| | III | 123 /197 (62.4%) | 20 /187 (10.7%) | 12 /185 (6.5%) | 17 /176 (9.7%) | 14 /171 (8.2%) |
| | IV | 11 /197 (5.6%) | 1 /187 (0.5%) | 1 /185 (0.5%) | 0 /176 (0.0%) | 1 /171 (0.6%) |
| | P-value† | NA | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| Six Minute Walk Test (m) | Summary at Visit | 230.5 ± 123.54 (163) | NA | 246.1 ± 160.25 (151) | NA | NA |
| | Change from Baseline to Visit | NA | NA | 27.5 ± 115.02 (133) | NA | NA |
| | P-Value‡ | NA | NA | 0.0067 | NA | NA |
| EQ5D | | | | | | |
| Mobility | Summary at Visit | 1.5 ± 0.51 (193) | 1.5 ± 0.54 (168) | 1.4 ± 0.54 (161) | NA | 1.5 ± 0.51 (147) |
| | Change from Baseline to Visit | NA | -0.1 ± 0.56 (166) | -0.1 ± 0.57 (159) | NA | -0.0 ± 0.63 (146) |
| | P-Value‡ | NA | 0.2174 | 0.0138 | NA | 0.6011 |
| Self-Care | Summary at Visit | 1.2 ± 0.45 (193) | 1.3 ± 0.52 (168) | 1.2 ± 0.47 (161) | NA | 1.3 ± 0.49 (148) |
| | Change from Baseline to Visit | NA | 0.1 ± 0.42 (166) | 0.1 ± 0.49 (159) | NA | 0.1 ± 0.49 (147) |
| | P-Value‡ | NA | 0.0003 | 0.1953 | NA | 0.0451 |
| Usual Activities | Summary at Visit | 1.5 ± 0.61 (193) | 1.6 ± 0.67 (159) | 1.5 ± 0.63 (160) | NA | 1.5 ± 0.62 (148) |
| | Change from Baseline to Visit | NA | 0.1 ± 0.61 (157) | -0.0 ± 0.67 (158) | NA | 0.0 ± 0.68 (147) |
| | P-Value‡ | NA | 0.0505 | 0.4750 | NA | 0.5431 |

**Table 7: CENTERA Study #2014-03: Effectiveness Endpoints through 1 Year (VI Population*, N=197)**

| | | Baseline | Discharge | 30 Days | 6 Months | 1 Year |
|---|---|---|---|---|---|---|
| Pain / Discomfort | Summary at Visit | 1.6 ± 0.60 (193) | 1.4 ± 0.55 (166) | 1.5 ± 0.56 (161) | NA | 1.5 ± 0.61 (147) |
| | Change from Baseline to Visit | NA | -0.2 ± 0.67 (164) | -0.1 ± 0.60 (159) | NA | -0.1 ± 0.66 (146) |
| | P-Value‡ | NA | 0.0004 | 0.0352 | NA | 0.3190 |
| Anxiety / Depression | Summary at Visit | 1.3 ± 0.52 (192) | 1.3 ± 0.49 (167) | 1.3 ± 0.51 (160) | NA | 1.3 ± 0.56 (147) |
| | Change from Baseline to Visit | NA | -0.1 ± 0.50 (165) | -0.1 ± 0.55 (158) | NA | 0.0 ± 0.57 (145) |
| | P-Value‡ | NA | 0.0858 | 0.2495 | NA | 0.8846 |
| Overall State | Summary at Visit | 62.0 ± 16.35 (192) | 66.6 ± 17.20 (168) | 68.0 ± 16.96 (161) | NA | 67.3 ± 17.94 (146) |
| | Change from Baseline to Visit | NA | 5.1 ± 17.79 (166) | 6.0 ± 17.11 (158) | NA | 5.5 ± 20.54 (145) |
| | P-Value‡ | NA | 0.0003 | <0.0001 | NA | 0.0015 |
| Echocardiographic measures | | | | | | |
| Paravalvular Regurgitation | None | NA | 80 /169 (47.3%) | 82 /160 (51.3%) | 86 /151 (57.0%) | 86 /137 (62.8%) |
| | Trace | NA | 15 /169 (8.9%) | 17 /160 (10.6%) | 14 /151 (9.3%) | 13 /137 (9.5%) |
| | Mild | NA | 68 /169 (40.2%) | 56 /160 (35.0%) | 50 /151 (33.1%) | 37 /137 (27.0%) |
| | Mild-Moderate | NA | 5 /169 (3.0%) | 4 /160 (2.5%) | 1 /151 (0.7%) | 1 /137 (0.7%) |
| | Moderate | NA | 1 /169 (0.6%) | 1 /160 (0.6%) | 0 /151 (0.0%) | 0 /137 (0.0%) |
| | Moderate-Severe | NA | 0 /169 (0.0%) | 0 /160 (0.0%) | 0 /151 (0.0%) | 0 /137 (0.0%) |
| | Severe | NA | 0 /169 (0.0%) | 0 /160 (0.0%) | 0 /151 (0.0%) | 0 /137 (0.0%) |

**Table 7: CENTERA Study #2014-03: Effectiveness Endpoints through 1 Year (VI Population*, N=197)**

| | | Baseline | Discharge | 30 Days | 6 Months | 1 Year |
|---|---|---|---|---|---|---|
| Total Aortic Regurgitation | None | 37 /168 (22.0%) | 72 /183 (39.3%) | 71 /165 (43.0%) | 77 /156 (49.4%) | 83 /147 (56.5%) |
| | Trace | 23 /168 (13.7%) | 33 /183 (18.0%) | 31 /165 (18.8%) | 24 /156 (15.4%) | 22 /147 (15.0%) |
| | Mild | 92 /168 (54.8%) | 71 /183 (38.8%) | 58 /165 (35.2%) | 54 /156 (34.6%) | 40 /147 (27.2%) |
| | Mild-Moderate | 12 /168 (7.1%) | 6 /183 (3.3%) | 4 /165 (2.4%) | 1 /156 (0.6%) | 2 /147 (1.4%) |
| | Moderate | 4 /168 (2.4%) | 1 /183 (0.5%) | 1 /165 (0.6%) | 0 /156 (0.0%) | 0 /147 (0.0%) |
| | Moderate-Severe | 0 /168 (0.0%) | 0 /183 (0.0%) | 0 /165 (0.0%) | 0 /156 (0.0%) | 0 /147 (0.0%) |
| | Severe | 0 /168 (0.0%) | 0 /183 (0.0%) | 0 /165 (0.0%) | 0 /156 (0.0%) | 0 /147 (0.0%) |
| Effective Orifice Area ($cm^2$) | Summary at Visit | 0.7 ± 0.20 (146) | 1.9 ± 0.48 (143) | 1.9 ± 0.43 (145) | 1.8 ± 0.42 (136) | 1.7 ± 0.42 (129) |
| | Change from Baseline to Visit | NA | 1.2 ± 0.43 (116) | 1.2 ± 0.40 (113) | 1.1 ± 0.41 (110) | 1.0 ± 0.40 (100) |
| | P-Value‡ | NA | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| Indexed Effective Orifice Area ($cm^2/m^2$) | Summary at Visit | 0.4 ± 0.12 (146) | 1.1 ± 0.29 (143) | 1.1 ± 0.28 (145) | 1.1 ± 0.27 (136) | 1.0 ± 0.27 (129) |
| | Change from Baseline to Visit | NA | 0.7 ± 0.26 (116) | 0.7 ± 0.26 (113) | 0.7 ± 0.26 (110) | 0.6 ± 0.25 (100) |
| | P-Value‡ | NA | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| Mean Aortic Valve Gradient (mmHg) | Summary at Visit | 40.6 ± 13.32 (185) | 8.2 ± 3.23 (186) | 7.2 ± 2.81 (166) | 7.5 ± 2.95 (161) | 8.1 ± 4.72 (147) |
| | Change from Baseline to Visit | NA | -32.5 ± 12.91 (178) | -34.2 ± 13.36 (159) | -33.7 ± 13.79 (152) | -32.7 ± 14.07 (139) |
| | P-Value‡ | NA | <0.0001 | <0.0001 | <0.0001 | <0.0001 |

Source: Table 3.4 based on data extracted 18JAN2018 and run on 25JAN2018
Note: Summary statistics: Categorical measures – n/N (%) Continuous measures - mean ± SD (n)
* Subject CNT 0354 014 was removed from VI population for this analysis due explant on the same day as implant procedure
† P-value compares the NYHA at follow-up to baseline using a Fisher's Exact Test.
‡ The p-value is from a two-sided paired t-test with the null hypothesis that there is no change from baseline.

### 1.3.2 CENTERA Study #2012-03

CENTERA study #2012-03 is a non-randomized, prospective, multicenter trial to assess the safety and device success of the Edwards CENTERA THV System (Model 9500G) in high surgical risk patients (STS Score ≥ 8) with symptomatic, severe AS who are indicated for AVR.

#### 1.3.2.1 Study Results

From February 18, 2013 through August 23, 2013 there were 34 high surgical risk patients enrolled. A database extract of September 6, 2016 was used for this report. Mean age was 82.7 ± 4.6 years with a Logistic EuroSCORE of 22.7 ± 13.0 and STS Score of 7.1 ± 3.5. The CENTERA THV was implanted in 32 out of 34 patients (94.1%). With regard to the other two patients, one patient was converted to SAVR after the left ventricle was perforated by a guidewire; the procedure was initiated for the other patient but valve implantation was not attempted due to decline in the patient condition prior to introduction of the study device. The two patients who did not receive the study implant died, resulting in a 30-day all-cause mortality rate of 5.9% in the AT population. Of the 32 patients in whom the valve was implanted (VI population), there were no deaths at 30 days. These rates are consistent with the study hypothesis of <10% mortality at 30-days post-index procedure.

Of the 32 enrolled patients in the VI population, 30 patients received a 26mm CENTERA THV (93.8%), and the remainder received the 23mm valve (6.3%). The procedure was performed under conscious sedation for 21/32 patients (65.6%). Predilation BAV was performed in all patients as specified per protocol and post-dilation was performed in 15/32 patients (46.9%). The final valve deployment position was correct at the intended site in 31/32 patients (96.9%). In one patient, the final position of the valve was more ventricular than intended, but the valve did not migrate or embolize. No valve-in-valve procedures were performed.

Follow-up evaluations are performed at discharge, 30 days, 6 months, and annually through 5 years. Three-year follow-up results are provided below.

- KM estimate for all-cause mortality at 3 years was 29.9% (AT Population)
    - A total of 10 patients died; 5 deaths were due to cardiovascular causes and 5 deaths were considered non-cardiovascular related.
- At 3 years, the incidence of CEC-adjudicated events was:
    - 2.9% for MI (n=1/34)
    - 5.9% for all stroke (n=2/34)
    - 14.7% for life-threatening or disabling bleeding (n=5/34)
    - 8.8% for vascular access related complications (n=3/34)
    - 11.8% for AKI (n=4/34)
    - 2.9% for SVD requiring repeat procedure (n=1/34)

The CEC determined that there were no events of arrhythmia, prosthetic valve endocarditis, prosthetic valve thrombosis, valve embolization, valve migration and coronary artery obstruction

requiring intervention through 3 years.

At every visit, the vast majority of patients with available NYHA data showed improvement from baseline. Through 3 years of follow-up, there was an improvement in NYHA Class in 15 of 21 patients evaluated while the remaining 6 remained in the same NYHA Class from baseline. There were no patients with worsened NYHA functional status through 3 years.

Echocardiographic endpoints were analyzed by a core laboratory. At all visits, PVL was ≤ mild in most patients. Moderate PVL was reported for 2 patients (9.1%) at discharge, and 1 patient (4.3%) at 30 days; no patients had severe PVL at any post-procedure time point. Through 3 years of follow-up, there were no cases of > mild PVL among 12 patients evaluated. The low incidence of PVL in the analyzed set of patients demonstrates the performance of the Edwards CENTERA THV.

The mean aortic valve (AV) gradient decreased from 33.4 ± 8.5 mmHg from baseline to 7.3 ± 1.9 mmHg at discharge, 7.0 ± 2.8 mmHg at 30 days, 7.5 ± 2.5 mmHg at 1 year, 8.7 ± 5.1 mmHg at 2 years, and 7.5 ± 2.7 mmHg at 3 years. The reduction in mean gradient from baseline at each visit was statistically significant.

### 1.3.3 CENTERA Study #2010-08

The purpose of this early feasibility study was to evaluate the safety and initial performance of the Edwards Self-Expanding THV with transarterial delivery system and accessories in symptomatic patients with severe calcific AS requiring AVR who were at high risk for open chest surgery due to existing co-morbidities.

#### 1.3.3.1 Study Results

A total of 19 patients were enrolled in two phases between November 2010 and October 2012 at Asklepios Klinik in Hamburg, Germany. In phase 1, under protocol version 001, 5 patients were enrolled in November and December 2010 and received valve model 9500TFX size 26 mm. In phase 2, under protocol version 002, an additional 14 patients were enrolled between June 2012 and October 2012 and received valve model 9500G sizes 23 mm (n=1) and 26 mm (n=13).

The CENTERA THV model 9500TFX and delivery systems were obsoleted and replaced with the newer CENTERA THV model 9500G which incorporated changes in frame design and pericardial tissue leaflet treatment. Clinical outcomes in patients implanted with CENTERA THV model 9500TFX in Phase 1 (n=5) are not comparable to those obtained with the newer CENTERA THV model 9500G in Phase 2 (n=14). Statistical analysis of safety and effectiveness were conducted for the 14 patients implanted with the CENTERA THV model 9500G.

The primary safety endpoint for this study was freedom from death at 30 days after the implant procedure.

- There were no patient deaths at 30 days among the initial 5 patients.
- In the subsequent cohort of 14 patients there was 1 patient death at 30 days for a KM estimate for all-cause mortality at 30 days of 7.1%. This rate is consistent with the study

hypothesis of <10% mortality at 30-days post-index procedure.

- At 4 years, the incidence of all site-reported adverse events for the 14-patient cohort was:
  - 7.1% for bleeding
  - 7.1% for all stroke
  - 21.4% for heart failure
  - 7.1% for renal failure

There were no unanticipated adverse events reported.

Through 1 year of follow-up, 8 of 10 patients showed improvement over baseline in NYHA functional class while 2 patients remained the same. There were no patients with worsened NYHA Class. In 8 patients evaluated at 3 years, improvement in NYHA Class was observed in 7 and 1 patient remained the same.

At discharge, 13 of 14 patients had mild or less PVL and 1 patient had moderate PVL. By 1 year follow-up, 8 of 9 patients had none/trace PVL and 1 patient presented with moderate PVL.

The mean AV gradient decreased from 43.4 ± 12.64 mmHg at baseline to 10.6 ± 3.37 mmHg at discharge, 10.4 ± 2.67 mmHg at 30 days, 9.6 ± 4.75 mmHg at 6 months, 10.8 ± 3.38 mmHg at 1 year, 13.3 ± 3.74 mmHg at 2 years, 16.3 ± 7.77 mmHg at 3 years and 12.0 mmHg at 4 years. The reduction in mean gradient from baseline at each visit to 2 years was statistically significant ($p < 0.001$ through 1 year and $p = 0.0117$ at 2 years).

## 2 STUDY OBJECTIVE

Following discontinuation of the CENTERA program, the objective of this study is to monitor the safety and valve performance of the Edwards CENTERA THV System in patients with symptomatic, severe, calcific AS who are at intermediate operative risk for SAVR.

## 3 STUDY DESIGN

This is a prospective, single-arm, multicenter study. Enrollment of 750 subjects with symptomatic, severe, calcific AS was planned at up to 65 US sites; enrollment has been closed with 101 subjects enrolled at 23 sites. Up to two roll-in subjects were allowed per site; roll-in subjects were not counted towards the enrolled sample size.

## 4 STUDY DEVICES

The CENTERA THV System, model 9551S, consists of a THV that is pre-attached to the delivery system and protected within a loading capsule. The THV and delivery system are supplied together in one package.

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

## 4.1 CENTERA THV

The CENTERA THV is composed of a self-expanding, radiopaque, Nitinol frame with trileaflet bovine pericardial tissue, and polyethylene terephthalate (PET) fabric. The tissue leaflets are treated with a proprietary process that allows the valve to be stored dry.

The CENTERA THV, available in 23, 26 and 29 mm sizes, is intended to be implanted in a native annulus size range comparable to the CT measurements shown in **Table 8** below.

**Table 8: CENTERA THV Sizing Dimensions**

| CENTERA THV Size | 23 mm | 26 mm | 29 mm |
|---|---|---|---|
| Native Annulus Perimeter-Derived Diameter | 18-21 mm | 21-24 mm | 24-27 mm |
| Native Annulus Perimeter | 56.5-66.0 mm | 66.0-75.4 mm | 75.4-84.8 mm |
| Native Annulus Area | 254-346 $mm^2$ | 346-452 $mm^2$ | 452-573 $mm^2$ |
| Minimum Access Vessel Diameter | 5.5 mm | 5.5 mm | 5.5 mm |

## 4.2 CENTERA Delivery System

The delivery system is designed to be used to deliver the THV to the implant site via the transfemoral artery. The system has a tapered distal tip which facilitates valve crossing, as well as a flex section which facilitates system tracking and positioning.

The recommended minimum femoral-iliac vessel diameters for introduction of the CENTERA THV system are shown in . Recommended vessel sizing is for use only with the 14F expandable sheath provided by Edwards.

The delivery system has an integrated battery powered (6V total) motorized handle designed to advance or retract the delivery capsule for loading or deploying of the THV, respectively.

**NOTE**: The handle is protected against fluids (drip-proof equipment IPX1). The handle is not suitable for use in the presence of a flammable anesthetic mixture. The handle operates in a continuous mode and is internally battery powered. The system constitutes a Type CF Applied Part.

## 4.3 Edwards Dilator Kit

The Edwards dilator kit contains a set of hydrophilically coated tapered dilators. The 22F dilator is used to pre-dilate the expandable portion of the Edwards expandable sheath.

## 4.4 Edwards eSheath Introducer

Edwards 14F eSheath Introducer is used to introduce the CENTERA delivery system into the vasculature.

# 5 STUDY OUTCOMES

The following outcomes will be evaluated:

1. Mortality at 30 days, 1 year and annually (up to 10 years)
2. Stroke at 30 days, 1 year and annually (up to 10 years)
3. Aortic valve reintervention at 30 days, 1 year and annually (up to 10 years)
4. SVD at years 1-5, 7 and 10
5. Hemodynamic valve performance evaluation by echocardiography including AV stenosis and AV regurgitation (paravalvular & central) at 30 days, and years 1-5, 7 and 10.

# 6 STUDY POPULATION

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

## 6.1 Inclusion Criteria

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

1. Severe, calcific AS meeting the following transthoracic echocardiogram (TTE) criteria:
   - Aortic Valve Area (AVA) ≤ 1.0 $cm^2$ OR AVA index ≤ 0.6 $cm^2/m^2$
   - Jet velocity ≥ 4.0 m/s OR mean gradient ≥ 40 mmHg
2. NYHA functional class ≥ II
3. Judged by the Heart Team to be at intermediate risk for open surgical therapy (i.e., predicted risk of surgical mortality ≥ 3% and < 8% at 30 days, based on the STS risk score and other clinical co-morbidities unmeasured by the risk calculator)
4. The subject has been informed of the nature of the study, agrees to its provisions and has provided written informed consent as approved by the Institutional Review Board (IRB)/ Ethics Committee (EC) of the respective clinical site.

## 6.2 Exclusion Criteria

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

1. Native aortic annulus size unsuitable for sizes 23, 26 or 29 mm CENTERA THV based on 3D imaging analysis
2. Aortic valve is unicuspid, bicuspid or non-calcified
3. Pre-existing mechanical or bioprosthetic valve in any position. (Of note, mitral ring is not an exclusion).
4. Known hypersensitivity to Nitinol (nickel or titanium)
5. Severe aortic regurgitation (> 3+)

6. Severe mitral regurgitation (> 3+) or ≥ moderate stenosis
7. Ventricular dysfunction with left ventricular ejection fraction (LVEF) < 30%
8. Cardiac imaging (echocardiography, computed tomography (CT) and/or magnetic resonance imaging (MRI)) evidence of intracardiac mass, thrombus or vegetation
9. Evidence of an acute MI ≤ 30 days before the valve implant procedure
10. Subjects with planned concomitant ablation for atrial fibrillation
11. Hypertrophic cardiomyopathy with obstruction (HOCM)
12. Coronary anatomy that increases the risk of coronary artery obstruction post-TAVR
13. Complex coronary artery disease (CAD):
    a. Unprotected left main coronary artery
    b. SYNTAX score > 32 (in the absence of prior revascularization)
    c. Heart Team assessment that optimal revascularization cannot be performed
14. Iliofemoral vessel characteristics that would preclude safe placement of the introducer sheath.
15. Significant abdominal or thoracic aortic disease that would preclude safe passage of the delivery system
16. Active bacterial endocarditis within 180 days of the valve implant procedure
17. Stroke or TIA within 90 days of the valve implant procedure
18. Symptomatic carotid or vertebral artery disease or successful treatment of carotid stenosis within 30 days of the valve implant procedure
19. Severe lung disease (Forced Ejection Volume 1 (FEV1) < 50% predicted) or currently on home oxygen
20. Severe pulmonary hypertension (e.g., pulmonary artery systolic pressure ≥ 2/3 systemic pressure)
21. Hemodynamic or respiratory instability requiring inotropic support, mechanical ventilation or mechanical heart assistance within 30 days of the valve implant procedure
22. History of cirrhosis or any active liver disease
23. Renal insufficiency (estimated glomerular filtration rate (eGFR) < 30 mL/min per the Cockcroft-Gault formula) and/or renal replacement therapy at the time of screening
24. 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
25. Inability to tolerate or condition precluding treatment with antithrombotic therapy during or after the valve implant procedure
26. Absolute contraindications or allergy to iodinated contrast that cannot be adequately treated with pre-medication
27. Significant frailty as determined by the Heart Team (after objective assessment of frailty parameters)
28. Immobility that would prevent completion of study procedures (e.g., six-minute walk tests, etc.)

29. Subject refuses blood products
30. Body mass index (BMI) > 50 kg/$m^2$
31. Estimated life expectancy < 24 months
32. Positive urine or serum pregnancy test in female subjects of childbearing potential
33. Currently participating in an investigational drug or another device study. Note: Trials requiring extended follow-up for products that were investigational, but have since become commercially available, are not considered investigational trials. Observational studies are not considered exclusionary.

# 7 STUDY PROCEDURES

## 7.1 Informed Consent

The study investigator(s) and support staff will approach subjects with symptomatic, severe calcific AS who meet general requirements to assess their interest in participating in the study by providing them an overview of the study including the background, risks, benefits and study procedures. If subjects are interested in participating in the study, the subject will sign the IRB/EC-approved informed consent form (ICF) prior to any study-specific procedures being performed. All subjects consented should be entered into the study's Electronic Data Capture (EDC) system.

## 7.2 Screening

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

**Systems:**

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

**Risk:**

- STS Risk Score
- EuroSCORE II
- TAVR Risk Score

**Cardiopulmonary:**

- NYHA Functional Class
- Canadian Cardiovascular Society (CCS) status of angina
- 12-lead Electrocardiogram (ECG)
- TTE – Qualifying TTE must be performed within 90 days prior to the valve implant procedure.
- 3D Cardiac Imaging (CT, Transesophageal Echocardiogram (TEE) or cardiac MRI) with 3D reconstruction to determine AV annulus area. Qualifying cardiac imaging must be

performed within 1 year prior to the valve implant procedure.

- Iliofemoral CT Angiography, including thoracic and abdominal scan with visualization of iliac and femoral arteries. Iliofemoral CT Angiography must be performed within 1 year prior to the valve implant procedure.
- Left Heart Catheterization to assess the severity of AS and, if applicable, the severity of CAD. Qualifying catheterization must be performed within 1 year prior to the valve implant procedure.
- Pulmonary Function Test – only for subjects with a history of lung disease
- SYNTAX Score – only for subjects with significant native CAD

**Neurological:**

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

**Clinical Laboratory Tests:**

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

**Functional:**

- Frailty Index (5 Meter Walk Test, grip strength, Activities of Daily Living and serum Albumin)
- 6MWT
- QoL Questionnaires
    - KCCQ
    - EQ-5D-5L
    - SF-36

Candidates that have signed the ICF and do not meet the inclusion/exclusion criteria in **Section 6** will be considered a Screen Failure. All assessments performed and the eligibility criteria that were not met will be entered into the EDC.

Candidates that withdraw consent or expire prior to or after the Case Review but before the valve

implant procedure will also be considered a Screen Failure.

### 7.2.1 Case Review

Before a case is submitted for review, the site Principal Investigator and Heart Team will screen the subject for fundamental enrollment criteria. It is required that at least one site surgeon Investigator personally examine the subject to determine operative risk. Once fully screened and deemed an appropriate candidate, the site will submit the case for review and approval consideration by the Case Review Board.

- If the case is approved by the Case Review Board, the subject may be scheduled for the valve implant procedure.
- If the case is not approved, the subject's status will be considered a Screen Failure.

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

## 7.3 Procedure

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

The valve implant procedure will be considered to have started when the first interventional access-related puncture (arterial) is established. Performance of TEE does not by itself constitute start of procedure.

A subject will be considered enrolled in the study once the subject has signed the ICF and the valve implant procedure has begun, as defined above.

It is strongly encouraged that the procedure be performed within 14 days of case review approval.

Procedure assessments will include the following:

**Systems:**

- Medications: Antithrombotics only
- Adverse Events

**Cardiopulmonary:**

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

Study subjects will be continuously monitored clinically, hemodynamically, and electrocardiographically during the procedure 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 subject continues to meet all eligibility criteria.

### 7.3.1 Device Preparation

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

### 7.3.2 Antithrombotic Recommendations

**Table 9** outlines the recommended antithrombotic regimen.

**Table 9: Recommended Antithrombotic Regimen**

| | |
|---|---|
| **Pre-Valve Implant Procedure** | • Aspirin (ASA) 81-100 mg QD |
| | • Subjects with a bare metal stent (BMS) within one month or drug-eluting stent (DES) within 12 months should be continued on Clopidogrel/prasugrel prior to their implant procedure.<br>• Subjects in atrial fibrillation on warfarin should be bridged with low molecular weight (LMW) or unfractionated (UF) heparin prior to the implant procedure.<br>• Subjects with persistent or paroxysmal atrial fibrillation and not on anticoagulation will not be required to have a TEE to rule out left atrial (LA) thrombus prior to implant procedure. If intra-procedural TEE during TAVR reveals thrombus, implant procedure will be aborted and delayed until subject has been on warfarin or dabigatran for 30 days. Note: thrombus must be eliminated in order to proceed with TAVR.<br>• In subjects undergoing concomitant TAVR/Percutaneous Coronary Intervention (PCI), Clopidogrel loading with either 300 mg or 600 mg prior to the implant procedure is recommended in addition to ASA. |
| **Intraprocedural** | • Heparin will be given to achieve/ maintain activated clotting time (ACT) ≥ 250 sec. |
| **Post-Valve Implant Procedure** | **Category I for Stroke Risk:** No atrial fibrillation, no recent stents<br>• ASA 81 mg QD<br>• Clopidogrel 300 mg load within 6 hours of the implant procedure (either pre or post)<br>• Clopidogrel 75 mg QD for at least one month post-implant procedure |
| | **Category II for Stroke Risk:** No atrial fibrillation, recent stents<br>• ASA 81 mg QD<br>• Clopidogrel 75 mg QD should be continued after the implant procedure without interruption for at least one month post-BMS and 12 months post-DES |
| | **Category III for Stroke Risk:** Atrial fibrillation, no recent stents<br>• ASA 81 mg QD<br>• Subjects should be started on warfarin or dabigatran 24 hours post-TAVR if clinically safe and this should be continued for at least one month or indefinitely, if possible. If clinically safe, subjects started on warfarin should be bridged with UF or LMW heparin until INR therapeutic.<br>• If subjects are not a candidate for warfarin or dagibatran, Clopidogrel 75 mg QD can be considered as an alternative. |
| | **Category IV for Stroke Risk:** Atrial fibrillation, recent stents<br>• ASA 81 mg QD<br>• Clopidogrel 75 mg QD for at least one month post-BMS or 12 months post-DES<br>• Subjects should be started on warfarin or dabigatran 24 hours post-TAVR if clinically safe and continued indefinitely. If clinically safe, subject's being started on warfarin should be bridged with UF or LMW heparin until INR therapeutic. |

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

### 7.3.3 Antibiotic Prophylaxis

Study subjects should be prophylactically treated for endocarditis per the recommendations of the AHA [32].

### 7.3.4 Contrast Media

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

### 7.3.5 Radiation Precautions

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

## 7.4 Post-procedure

The post-procedure time period is defined as the 48 hours after the subject exits the procedure room. Subsequent monitoring will continue according to institutional standard of care.

The following will be assessed during the post-procedure time period:

**Systems:**

- Medications: Antithrombotics only
- Adverse Events

**Cardiopulmonary:**

- 12-lead ECG

**Neurological:**

- NIHSS

All subjects should be assessed post-procedure to determine if there is evidence of neurological impairment. If symptoms of stroke are suspected, the NIHSS should be performed.

**Clinical Laboratory Tests:**

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

## 7.5 Discharge

Discharge is the actual date and time the subject is discharged. For subjects discharged within 48 hours of exiting the procedure room, it is not required to repeat tests collected during the Post-

Procedure period that are also required for the discharge visit. If the subject was discharged over a weekend or holiday, the discharge assessments may be completed on the last weekday prior to discharge.

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

**Systems:**

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

**Cardiopulmonary:**

- NYHA functional class
- TTE

**Neurological:**

- NIHSS

All subjects should be assessed to determine if there is evidence of neurological impairment. If symptoms of stroke are suspected, the NIHSS should be performed.

**Clinical Laboratory Tests:**

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

## 7.6 Follow-up

The day of the procedure will be considered Day 0 and will be used to schedule all subsequent visits and calculate visit windows.

### 7.6.1 30 Days (+ 7 days)

The following assessments will be conducted:

**Systems:**

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

**Cardiopulmonary:**

- NYHA functional class
- 12-lead ECG
- TTE

**Neurological:**

- NIHSS
- mRS
- MMSE

**Clinical Laboratory Tests:**

- WBC, Hgb, and platelet count
- Creatinine

**Functional:**

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

### 7.6.2 1 Year (+ 30 days)

The following assessments will be conducted:

**Systems:**

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

**Cardiopulmonary:**

- NYHA functional class
- 12-lead ECG
- TTE

**Neurological:**

- MMSE

The following assessments should be completed for all subjects diagnosed with stroke after the procedure:

- NIHSS
- mRS

**Functional:**

- 6MWT
- QoL Questionnaires

- KCCQ
- EQ-5D-5L
- SF-36

#### 7.6.3 2 through 5, 7 and 10 years (+ 45 days)

The following assessments will be conducted annually:

- Adverse Events
- TTE

#### 7.6.4 6, 8 and 9 years (+ 45 days)

Adverse events will be assessed annually by telephone or office visit.

### 7.7 Imaging Assessments

Imaging performed during the course of the study should follow imaging manual of operations:

- Echo Manual of Operations
- CT Manual of Operations

### 7.8 Neurological Assessments

Every effort should be made to have a neurologist (or neurology fellow) perform the NIHSS and mRS assessments. If it is not possible to have the neurologist/fellow perform the assessments within the protocol-specified visit window, a certified study team member may perform the assessments. For all subjects diagnosed with a new stroke after the procedure start, a follow-up mRS assessment should be performed 90 days (± 30 days) after stroke onset to assess stroke disability (visit or phone assessment is acceptable). If the 90-day post-stroke assessment is scheduled to occur within 30 days of a protocol-specified visit, the mRS does not need to be repeated.

### 7.9 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 subjects' 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). Subject questionnaires will be IRB/EC-approved prior to subject administration.

Investigational staff will administer subject questionnaires to study subjects. Subjects will be instructed to complete each questionnaire at visits specified in **Section 7**. Investigational sites should retain the completed questionnaire in the subjects' source documents.

### 7.10 Subject Discontinuation

Every subject should be encouraged to remain in the study until they have completed the protocol required follow-up. Site personnel should make all reasonable efforts to locate and communicate with the subject at each visit time point. If the subject has missed multiple visits (with multiple attempts to contact), the subject may be considered lost-to-follow-up.

Subjects are considered discontinued when they leave the study after they have been enrolled. Potential reasons for early discontinuation include:

- Study Device Never Implanted: Subjects considered enrolled but did not receive a study valve will be followed for 30 days or until resolution of any adverse events related to the valve implant procedure and then exited from the study.
- Study Device Explanted: Subjects who have a surgical reintervention where the CENTERA valve is explanted will be followed for 30 days post-reintervention or until resolution of any adverse events related to the procedure and then exited from the study. Note: Subjects that have a BAV or valve-in-valve procedure will continue to be followed for the duration of the study.

If a subject discontinues prematurely, all attempts should be made to have the subject come into the clinic for an exit visit to complete the assessments that would have occurred at the next scheduled visit. At a minimum, a telehealth visit should occur to assess adverse events. An exit form indicating the reason for discontinuation will be completed for all subjects. Subjects who discontinue prematurely will be included in the analysis of results and will not be replaced.

For subjects that are lost-to-follow-up or withdraw early, Edwards may request the site to search the Social Security Death Index and/or other death registries and may request the site to obtain the death certificate, if applicable.

**Table 10** summarizes the subject assessments at each time point.

**Table 10: Schedule of Assessments**

| | Screening | Procedure | Post-Procedure | Discharge | 30 Days | 1 Year | 2-5, 7, 10 Years | 6, 8, 9 Years [p] |
|---|---|---|---|---|---|---|---|---|
| Visit Window (days) | - 30 [a] | | + 2 [o] | | + 7 | + 30 | + 45 | + 45 |
| Informed Consent | X | | | | | | | |
| Medical History | X | | | | | | | |
| Physical Assessment | X | | | X | X | X | | |
| Medications: Antithrombotics | X | X | X | X | X | X | | |
| Adverse Events | | X | X | X | X | X | X | X |
| STS Risk Score | X | | | | | | | |
| EuroSCORE II | X | | | | | | | |
| TAVR Risk Score | X | | | | | | | |
| NYHA Functional Class | X | | | X | X | X | | |
| CCS Angina | X | | | | | | | |
| 12-lead ECG | X | | X | | X | X | | |
| TTE | X [b] | | | X [c] | X [c] | X [c] | X [c] | |
| TTE/Aortogram or TEE | | X | | | | | | |
| 3D Cardiac Imaging (CT, TEE or cMRI) | X [d] | | | | | | | |
| Iliofemoral CT Angiography | X [d] | | | | | | | |
| Left Heart Catheterization | X [d] | | | | | | | |
| Pulmonary Function Test | X [e] | | | | | | | |
| SYNTAX Score | X [f] | | | | | | | |
| NIHSS [g] | X | | X [h] | X [h] | X | X [i] | | |
| mRS [g,h] | X | | | | X | X [i] | | |
| MMSE | X | | | | X | X | | |
| WBC, Hgb, Platelet Count | X | | X | X | X | | | |
| PT or INR | X | | X | X | | | | |
| CK/CKMB and/or Troponins | X [j] | | | | | | | |
| eGFR | X | | | | | | | |
| Creatinine | X | | X | X | X | | | |
| Albumin, Total Bilirubin | X | | | | | | | |
| AST/ALT | X [k] | | | | | | | |
| Pregnancy test | X [l] | | | | | | | |
| Frailty Index | X [m] | | | | | | | |
| 6MWT | X | | | | X | X | | |

## Table 10: Schedule of Assessments

| | Screening | Procedure | Post-Procedure | Discharge | 30 Days | 1 Year | 2-5, 7, 10 Years | 6, 8, 9 Years [p] |
|---|---|---|---|---|---|---|---|---|
| Visit Window (days) | - 30 [a] | | + 2 [o] | | + 7 | + 30 | + 45 | + 45 |
| KCCQ | X | | | | X | X | | |
| EQ-5D-5L | X | | | | X | X | | |
| SF-36 | X | | | | X | X | | |
| Case Review | X [n] | | | | | | | |
| Valve Implant Procedure | | X | | | | | | |

a. Screening assessments will be completed within 30 days prior to valve implant procedure, unless otherwise noted.
b. Must be performed within 90 days prior to the valve implant procedure.
c. Must be performed per Echo Manual of Operations.
d. Must be performed within 1 year prior to the valve implant procedure.
e. Only for subjects with a history of lung disease.
f. Only for subjects with significant native CAD.
g. Every effort should be made to have a neurologist (or neurology fellow) perform the 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.
h. 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).
i. Only for subjects diagnosed with a stroke after the procedure.
j. Required ≤ 72 hours before the valve implant procedure.
k. Only required for subjects with chronic liver disease.
l. Only for female subjects of childbearing age (urine or serum)
m. Includes activities of daily living, 5 meter walk test, grip strength and albumin.
n. Case Review will be completed when all screening procedures have been completed, all inclusion/exclusion criteria have been fundamentally confirmed and the site is ready to present a case.
o. Post-procedure time period is defined as the 48 hours after the subject exits the procedure room.
p. Can be done by telephone or office visit.

# 8 ADVERSE EVENTS

## 8.1 Adverse Event Definitions

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

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

All relevant AEs will be reported by the Investigator and reviewed by Edwards in compliance with applicable regulations as indicated below **Section 8.3**.

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

- Led to death;
- Led to a serious deterioration in the health of the subject that:
  - Resulted in a 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 an SAE if they seriously jeopardize the subject and require immediate medical or surgical intervention to prevent one of the aforementioned outcomes.

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

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 subjects.

## 8.2 Investigator Assessment of AEs

If it is determined that an AE has occurred, the Investigator should obtain all the information required to complete the AE eCRF.

For each AE, the Investigator will determine whether the event is related to the device and/or the implant procedure, whether it was anticipated or not anticipated (based on the list of potential risks provided in **Section 9.2**) and whether the event meets the definition of an SAE or UADE as outlined in **Section 8.1**.

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

- **None:** The event is not associated with the device or implant procedure. There is no relation between the event and the device or implant procedure.
- **Unlikely Related:** The temporal sequence between the device or implant procedure and the event is such that the relationship is unlikely but not impossible or there is contradicting evidence that can provide plausible explanation of the study subject's condition.
- **Possibly Related:** The temporal sequence between the device or implant procedure and the event is such that the relationship is not unlikely or there is no contradicting evidence that can reasonably explain the study subject's condition. There is a possibility of any relation between the event and the device or implant procedure.
- **Definitely Related:** The temporal sequence is relevant or the event abates upon device removal or the event cannot be reasonably explained by the subject's condition or comorbidities. The event is related or most likely associated with the device or implant procedure.

All AEs must be followed until resolution or until a stable clinical outcome is reached or until the subject has exited the study.

### 8.3 AE Reporting Requirements

All AEs will be captured from the time of enrollment (start of valve implant procedure) through 1 year post-procedure . After 1 year post-procedure, only following events need to be captured:

- All AEs related to outcomes
- All AEs that are assessed or suspected to be device or implant procedure related
- All AEs that meet the criteria for an SAE irrespective of device or implant procedure relationship
- All AEs considered to be a UADE

See **Section 8.3.1** for events that are not required to be reported to Edwards.

Pre-existing medical conditions or symptoms reported prior to subject enrollment will not be recorded as an AE. In the event there is a worsening in the pre-existing medical condition that is relevant to the subject's clinical course related to the treatment of their AS 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.

All relevant AEs, SAEs and UADEs must be reported to Edwards **as soon as practical but no later than 10 working days of awareness**. Information must be entered into the EDC or when EDC is not available, reported via email to THV_Safety@edwards.com, copying the Edwards Safety Officer of the study.

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

- Study site
- Subject ID
- AE description
- Causal relationship to study device and implant procedure
- Aware date

The site will provide a copy of supporting documentation (example: admission history & physical, implant procedure reports, anesthesia records, discharge summary, echocardiogram and ECG reports, laboratory results, etc.) for all events related to endpoints and outcomes (see **Section 5**), device malfunctions, device- and procedure-related events and UADEs to Edwards (or designee). Source documentation may be requested by the Edwards Safety Officer for other AEs and SAEs on a case-by-case basis.

Enrolling sites must send to Edwards Clinical Safety, at a minimum, an admission history and physical, valve implant procedure report and discharge summary from index hospitalization along with relevant labs, echocardiographic and ECG reports for each subject enrolled in the study. This will be done irrespective of subject having any AE/SAE.

The Investigator is responsible for notifying the IRB/EC of SAEs, UADE and/or AEs, as required; UADEs must be reported 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/EC, local regulations, Edwards or FDA. A copy of all IRB/EC reports should be provided to Edwards (or designee).

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

### 8.3.1 Events that do not require reporting to the Sponsor

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

- Post-operative pain

- Post-anesthesia emesis, nausea or headache (within 24 hours of procedure)
- Electrolyte imbalance without clinical sequelae following procedure, even if requiring correction
- Pre-planned future surgical procedures not associated with the study procedure or device
- Low grade temperature increase (≤ 101°F or 38.5°C)
- Dizziness: Imprecise term commonly used to describe various symptoms such as faintness, giddiness, imbalance, lightheadedness, unsteadiness or vertigo without signs of TIA or stroke.
- Elevated WBC, 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.

### 8.4 Sponsor Assessment of AEs

All AEs will be reviewed by the Edwards Safety Officer. Each AE will be assessed as to its relationship to the study device and/or implant procedure, whether it was anticipated or not anticipated (based on the list of potential risks provided in **Section 9.2**) and whether it qualifies as an SAE or UADE as outlined in **Section 8.1**.

### 8.5 Device Malfunctions

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

Device malfunctions should be reported to Edwards **as soon as practical but no later than 10 working days of the site awareness of these malfunctions**.

# 9 RISKS AND BENEFIT ANALYSIS

## 9.1 Potential Benefits

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

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

## 9.2 Potential Risks

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

Potential risks associated with standard cardiac catheterization, BAV and use of anesthesia include but are not limited to:

- Abnormal lab values (including electrolyte imbalance)
- Acute myocardial infarction
- Allergic reaction to device materials, antithrombotic therapy or contrast medium or anesthesia
- Anemia
- Aneurysm
- Angina
- Arrhythmias including ventricular fibrillation (VF) and ventricular tachycardia (VT)
- Arteriovenous fistula
- Arthralgia
- Bleeding/bruising
- Cardiovascular injury including perforation or dissection of vessels, ventricle, myocardium or valvular structures that may require intervention
- Conduction system defect which may require a permanent pacemaker
- Cardiogenic shock/pulmonary edema
- Cerebrovascular accident
- Death
- Dissection: aortic or other vessels
- Embolization including air, calcific valve material, or thrombus
- Exercise intolerance or weakness
- Fever
- GI symptoms
- Headache
- Heart failure
- Hematologic dyscrasia
- Heart murmur
- Hematoma
- Hemorrhage requiring transfusion or intervention
- Hemorrhagic stroke
- Hepatic enzyme changes
- Hypotension or Hypertension
- Infection including septicemia and endocarditis

- Inflammation
- Ischemia or nerve injury
- Limb ischemia
- Myocardial infarction
- Myalgia
- Pain or changes at the access site
- Paralysis
- Perforation or rupture of cardiac structure
- Perforation or rupture of vessel
- Pericardial effusion/cardiac tamponade
- Permanent disability
- Peripheral nerve injury/paralysis
- Postoperative encephalopathy
- Pleural effusion
- Pulmonary edema
- Pseudoaneurysm
- Renal insufficiency or renal failure
- Reoperation
- Respiratory insufficiency or respiratory failure
- Restenosis
- Retroperitoneal bleed
- Shock
- Silent cerebral ischemia
- Stroke/transient ischemic attack, clusters or neurological deficit
- Syncope
- Thoracic bleeding
- Vasovagal response
- Vessel spasm
- Vessel thrombosis/occlusion
- Vessel trauma requiring surgical repair or intervention

In addition to the risks listed above, additional potential risks specifically associated with AVR and bioprosthetic heart valves include, but may not be limited to:

- Acute coronary occlusion
- Allergic/immunologic reaction to the implant
- Aortic annulus dissection/rupture/trauma
- Aortic valve insufficiency
- Aortic valve thrombosis/occlusion
- Atrial fibrillation/Atrial flutter
- Arteriovenous block
- Blood loss requiring blood transfusion
- Cardiac arrest
- Cardiac failure or low cardiac output
- Cardiogenic shock
- Cognitive impairment
- Conduction disturbance including AV block requiring pacemaker
- Device degeneration
- Device embolization
- Device explants
- Device migration or malposition requiring intervention
- Device thrombosis requiring intervention
- Device malfunction requiring intervention/surgery
- Emergency cardiac surgery
- Endocarditis
- Hemolysis
- Injury to aortic and/or mitral valve
- Mechanical failure of delivery system, and/or accessories
- Mediastinitis
- Mediastinal bleeding
- Mitral regurgitation
- Non-emergent reoperation
- Nonstructural dysfunction
- Peri-/Paravalvular leak/regurgitation (moderate to severe)
- Structural valve deterioration (wear,

fracture, calcification, leaflet tear/tearing from the stent posts, leaflet retraction, thickening, stenosis)
- Valve deployment in unintended location
- Valve regurgitation
- Valve stenosis
- Valve thrombosis

### 9.2.1 Risk Minimization

Product handling and implant procedure guidance are provided in the IFU and training manual, which will be used for device training to minimize risks associated with device use. All cases will be reviewed and approved prior to enrollment to confirm that the subject is an appropriate candidate for the investigational devices and Edwards representative(s) will be present during all implant procedures to provide device-related guidance. Additionally, efforts will be made to minimize risks through site/investigator selection and study management. 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.

## 10 STATISTICAL ANALYSIS

### 10.1 Analysis Populations

- The All Treated (AT) population is defined to include all enrolled subjects (see **Section 7.3**), whether or not the index procedure is completed.
- The Valve Implant (VI) population is the subset of the AT population consisting of all subjects who receive and retain the CENTERA valve upon leaving the procedure room. Subjects who are converted to SAVR during the procedure will not be part of the VI population.

Roll-in subjects will not be pooled with enrolled subjects for data analysis and will not be counted towards the enrolled sample size.

### 10.2 General Statistical Methodology

The study outcomes will be summarized with descriptive statistics as described below. No hypothesis testing will be performed.

- Time-to-event variables will be analyzed using the KM algorithm, with standard errors computed by Greenwood's formula. The number of subjects-at-risk will be computed at exact time points, without reference to any nominal follow-up windows.
- For continuous variables, summary statistics will include means, standard deviation and sample size.
- For ordinal variables, summary statistics will include counts and percentages and will be presented when appropriate.
- For categorical variables, summary statistics will include counts and percentages.

# 11 STUDY ADMINISTRATION

## 11.1 General Study Organization

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

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

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

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

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

## 11.2 Steering Committee

A Steering Committee will be selected to provide oversight and medical expertise to the study. Steering Committee activities will be defined in the Steering Committee Charter. Steering Committee activities ceased after enrollment closure.

## 11.3 Case Review Board

The Case Review Board is comprised of a subset of Investigators who are participating in the study. The role of the Case Review Board is to review submitted cases to determine if the subject is an appropriate candidate for the study, with a focus on confirming subject operative risk, valve sizing, appropriate vascular access, valve morphology and any relevant clinical factors impacting enrollment eligibility. Case Review Board activities ceased after enrollment closure.

## 11.4 Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will review study data, evaluate trends in reported adverse events and any potential changes in risk assessment, and make recommendations to Edwards regarding safety issues and risks to research subjects as well as the continuing validity and scientific merit of the study. DSMB activities are defined in the DSMB Charter. DSMB activities ceased after enrollment closure.

### 11.5 Clinical Events Committee

The CEC will adjudicate endpoint and outcome-related events (see **Section** 5) and provide assessment of SAEs and device/procedure-relatedness from enrollment through the primary endpoint. CEC activities are defined in the CEC Charter. CEC activities ceased after enrollment closure.

### 11.6 Echocardiographic Core Lab

Study subjects will receive an echocardiogram at the visits specified in **Section** 7. An echocardiographic 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.

### 11.7 Computed Tomography Core Lab

Study subjects will have a CT at the visits specified in **Section 7**. A CT core lab will be established to independently review and analyze CT images (and MRI images, if any). 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.

### 11.8 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 analysis.

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.

### 11.9 Histopathology

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

### 11.10 Site Personnel 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 log.

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

Ongoing training may be provided in one of the following formats by Edwards or its designee: live training sessions, teleconference, WebEx, online or read and review. Retraining may be

performed for sites who have demonstrated protocol or implant procedure compliance issues.

Documentation of site personnel qualifications and training should be maintained in the site's clinical study files and copies collected and forwarded to Edwards.

## 11.11 Device Management

### 11.11.1 Investigational Device

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

### 11.11.2 Device Storage

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

### 11.11.3 Device Accountability

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

## 11.12 Data Management

Edwards will provide data management through a secure, password protected EDC system accessible via the Internet. A unique Subject ID will be assigned for each subject enrolled in the study. All pertinent data from the subject'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 personnel will occur remotely as well as during on-site monitoring. Data discrepancies will be queried and resolved through the EDC system.

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

## 11.13 Monitoring Procedures

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

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

### 11.14 Auditing

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

### 11.15 Publication Policy

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

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

## 12 ETHICAL AND REGULATORY CONSIDERATIONS

### 12.1 Applicable Regulations

This study will be conducted in compliance with the Title 21 CFR Parts 50, 56, 812, and Good Clinical Practices (GCP).

### 12.2 Institutional Review Board

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

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

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

### 12.3 Informed Consent

Edwards will provide a sample ICF to the Investigator to prepare for use at his/her site. The site-specific ICF, and any subsequent modifications, must be in agreement with current regulations

and guidelines and must be approved by Edwards prior to submission to the IRB/EC. The reviewing IRB/EC must approve the ICF before use at the site.

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

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

### 12.4 Confidentiality

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

### 12.5 Investigator Records

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

- Clinical study protocol and all amendments
- Signed Clinical Trial Agreement and any amendments
- IRB/EC approval letters, including continuing reviews and all amendments/changes
- IRB/EC approved informed consent documents
- All correspondence with another Investigator, IRB/EC, sponsor, 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 study:

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

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

### 12.6 Investigator Reports

In addition to AE reporting requirements discussed in **Section 8.3**, the following reports are

required:

- Withdrawal of IRB/EC Approval. Within 5 working days, the Principal Investigator will report a withdrawal of approval by the reviewing IRB/EC of the Investigator's part of an investigation to Edwards.
- Informed Consent. If an Investigator uses a device without obtaining informed consent, the Investigator shall report such use to Edwards and the reviewing IRB/EC within 5 working days after the use occurs.
- Progress Reports. The Principal Investigator will submit progress reports on the investigation to Edwards and the IRB/EC at least yearly.
- Final Report. Upon completion or termination of this Study, the Principal Investigator must submit a final written report to Edwards and the IRB/EC as required by the regulations. The report must be submitted within 3 months of completion or termination of the study.

### 12.7 Amending the Protocol

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

### 12.8 Protocol Deviations

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

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

## APPENDIX A. ABBREVIATIONS

| Abbreviation | Full Term |
|---|---|
| 6MWT | Six-Minute Walk Test |
| ACC | American College of Cardiology |
| ACT | Activated Clotting Time |
| AE | Adverse Event |
| AHA | American Heart Association |
| AKI | Acute Kidney Injury |
| ALT | Alanine Aminotransferase |
| ANOVA | Analysis of Variance |
| AR | Aortic Regurgitation |
| AS | Aortic Stenosis |
| ASA | Aspirin |
| AST | Aspartate Aminotransferase |
| AT | All Treated |
| ATT | Average Treatment effect for the Treated |
| AV | Aortic Valve |
| AVA | Aortic Valve Area |
| AVR | Aortic Valve Replacement |
| BAV | Balloon Aortic Valvuloplasty |
| BMI | Body Mass Index |
| BMS | Bare Metal Stent |
| CABG | Coronary Artery Bypass Graft |
| CAD | Coronary Artery Disease |
| CCS | Canadian Cardiovascular Society |
| CEC | Clinical Events Committee |
| CFR | Code of Federal Regulations |
| CI | Confidence Interval |
| CK | Creatine Kinase |
| CKMB | Creatine Kinase MB Isoenzyme |
| COPD | Chronic Obstructive Pulmonary Disease |
| CT | Computed Tomography |
| DES | Drug Eluting Stent |
| DM | Diabetes Mellitus |
| DoA | Delegation of Authority |
| DSMB | Data Safety Monitoring Board |
| EACTS | European Association for Cardio-Thoracic Surgery |
| EC | Ethics Committee |
| ECG | Electrocardiogram |

| Abbreviation | Full Term |
|---|---|
| eCRF | Electronic Case Report Form |
| eGFR | Estimated Glomerular Filtration Rate |
| EDC | Electronic Data Capture |
| EOA | Effective Orifice Area |
| EQ | EuroQol |
| ESC | European Society of Cardiology |
| ExCEED | A Prospective, Single-arm, Controlled, Multicenter Study to **E**stablish the Safety and Effectiveness of the **CE**NTERA THV System in Interm**ED**iate Risk Patients who have Symptomatic, Severe, Calcific, Aortic Stenosis Requiring Aortic Valve Replacement |
| FEV1 | Forced Expiratory Volume in 1 Second |
| FDA | Food and Drug Administration |
| Hgb | Hemoglobin |
| HOCM | Hypertrophic Obstructive Cardiomyopathy |
| ICF | Informed Consent Form |
| ICU | Intensive Care Unit |
| IDE | Investigational Device Exemption |
| IFU | Instructions for Use |
| INR | International Normalized Ratio |
| IRB | Institutional Review Board |
| KCCQ | Kansas City Cardiomyopathy Questionnaire |
| KM | Kaplan-Meier |
| LA | Left Atrial |
| LMW | Low Molecular Weight |
| LVEF | Left Ventricular Ejection Fraction |
| MACCE | Major Adverse Cardiovascular and Cerebrovascular Events |
| MI | Myocardial Infarction |
| MMSE | Mini Mental State Examination |
| MR/MRI | Magnetic Resonance / Magnetic Resonance Imaging |
| mRS | Modified Rankin Scale |
| NIHSS | National Institutes of Health Stroke Scale |
| NYHA | New York Heart Association |
| OPG | Objective Performance Goal |
| PARTNER | Placement of AoRtic TranNscathetER |
| PCI | Percutaneous Coronary Intervention |
| PET | Polyethylene Terephthalate |
| Plt | Platelets |
| PPM | Patient Prosthesis Mismatch |
| PT | Prothrombin Time |
| PVL | Paravalvular Leak |

| Abbreviation | Full Term |
|---|---|
| QD | Every Day / Daily |
| QoL | Quality of Life |
| SAVR | Surgical Aortic Valve Replacement |
| SAE | Serious Adverse Event |
| SF | Short Form |
| STS | Society of Thoracic Surgeons |
| SVD | Structural Valve Deterioration |
| TAVR | Transcatheter Aortic Valve Replacement |
| TEE | Transesophageal Echocardiogram |
| THV | Transcatheter Heart Valve |
| TIA | Transient Ischemic Attack |
| TTE | Transthoracic Echocardiogram |
| UADE | Unanticipated Adverse Device Effect |
| UF | Unfractionated Heparin |
| VF | Ventricular Fibrillation |
| VI | Valve Implant |
| VT | Ventricular Tachycardia |
| WBC | White Blood Cell |

## APPENDIX B. DEFINITIONS

| Term | Definition | Reference/ Justification |
|---|---|---|
| 6 Minute Walk Test (6MWT) | 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: https://www.rheumatology.org/I-Am-A/Rheumatologist/Research/Clinician-Researchers/Six-Minute-Walk-Test-SMWT | ATS |
| Access Site | Any location (arterial or venous) traversed by a guidewire, a catheter or a sheath for TAVR | VARC-1 [33] |
| Access Site Related Complication | Any adverse clinical consequence possibly associated with any of the access sites used during the procedure<br>Planned repair of access site entry portals are not considered access site-related complications. | VARC-1, VARC-2 [34] |
| Acute Kidney Injury (AKI) | AKI is defined by an abrupt decrease in kidney function<br>• Reportable AKI is for any creatinine with an increase in serum creatinine to > 150% of baseline, OR<br>• increase of ≥ 0.3 mg/dL compared to baseline within 48 hours of index procedure, OR<br>• Urine output < 0.5 mL/kg per hour for > 6 but < 12 hours<br>Patients receiving renal replacement therapy (dialysis, hemodialysis, peritoneal dialysis, hemofiltration, transplant therapy) are considered to meet Stage 3 AKI criteria.<br>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.<br>Note: AKI stage will be determined per VARC-2 criteria. | AKIN / KDIGO / VARC-2 / Sponsor |
| Adverse Event (AE) | Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device | ISO 14155-1:2011<br>GCP |
| Angina / Cardiac Chest Pain | Chest pain due to myocardial ischemia caused by an imbalance between myocardial blood supply and oxygen demand. | Sponsor |

<table>
<tr><th>Term</th><th>Definition</th><th>Reference/ Justification</th></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 a normal pace</td></tr>
<tr><td>IV</td><td>Inability to carry on any physical activity without discomfort. Angina syndrome may be present at rest</td></tr>
</table>
</td><td>Canadian Cardiovascular Society</td></tr>
<tr><td>Aortic Dissection</td><td>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).</td><td>Sponsor</td></tr>
<tr><td>Aortic Stenosis, Native</td><td>Aortic stenosis is classified as “severe” when the following are present:<ul><li>Jet velocity ≥ 4.0 m/s</li><li>Mean gradient ≥ 40 mmHg</li><li>Valve area ≤ 1.0 $cm^2$</li><li>Valve area index ≤ 0.6 $cm^2/m^2$</li></ul></td><td>2014 AHA/ACC</td></tr>
<tr><td>Arrhythmia / Conduction System Injury (Defect)</td><td>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.<br>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).</td><td>Sponsor</td></tr>
</table>

| Term | Definition | Reference/ Justification |
|---|---|---|
| Atrial Fibrillation | Atrial fibrillation is rapid irregular heart rhythm characterized by rapid and irregular beating of atria with or without associated ventricular fibrillation and has ECG characteristics of atrial fibrillation and lasts sufficiently long to be recorded on a 12-lead ECG, or at least 30 seconds on a rhythm strip.<br>The type of atrial fibrillation includes:<br>• Paroxysmal atrial fibrillation: Atrial fibrillation that terminates spontaneously or with intervention within 7 days of onset. Episodes may recur with variable frequency.<br>• Persistent atrial fibrillation: Continuous atrial fibrillation that is sustained >7 days or requires medical (rate/rhythm control) or surgical intervention (Ex: ablation, cardioversion or Maze procedure).<br>• Permanent AF: Permanent AF is used when there has been an inability to restore and/or maintain sinus rhythm with medical and/or surgical intervention. | Sponsor [35] |
| 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.<br>Type 1: valve with one raphe<br>Type 2: valve with two raphes | [36] |

| Term | Definition | Reference/ Justification |
|---|---|---|
| Bioprosthetic Valve Dysfunction (BVD) | Bioprosthetic valve dysfunction (BVD) can be either non-structural or structural:<br><br>**Non-structural causes of BVD** (BVD due to extrinsic causes or processes unrelated to intrinsic function of valve leaflets) are defined as any of the following:<br>• Paravalvular leak (PVL)<br>• Endocarditis<br>• Patient-prosthesis mismatch (moderate or severe per Valve Academic Research Consortium-2 (VARC 2) definitions) at discharge<br><br>**Structural BVD** should be defined as follows (regardless of whether or not findings drive therapy):<br>• **Bioprosthetic valve hemodynamic dysfunction (BVHD)**<br>  • 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.<br>  • Moderate BVHD – Mean gradient ≥ 20 mmHg, and/or new or progressive moderate intra-prosthetic AR<br>  • Severe BVHD – Mean gradient ≥ 40 mmHg, and/or new or progressive severe intra-prosthetic AR<br>• **Bioprosthetic valve structural deterioration (BVSD)**<br>  • Anatomic imaging evaluation (echocardiography or CT) or autopsy findings demonstrate persistent bioprosthetic leaflet pathology related to<br>  i. structure (leaflet tears, etc.)<br>  ii. abnormal thickness without mobility change<br>  iii. mobility restriction (RLM)<br>  iv. calcification<br>• **Bioprosthetic Valve Failure (BVF)**<br>  • Referral for aortic valve re-intervention (valve-in-valve) or reoperation for progressive BVHD and/or BVSD<br>  • Valve-related death<br>  • An unexplained death following diagnosis of BVD in any of the above stages<br>  • BVSD observed at autopsy likely related to cause of death<br>  • The presence of severe hemodynamic dysfunction (i.e., mean gradient ≥ 40 mmHg, and/or new or progressive severe intra-prosthetic regurgitation), whether or not the patient is referred for reintervention or reoperation | FDA |

| Term | Definition | Reference/ Justification |
|---|---|---|
| Bleeding | Overt bleeding is defined as clinically obvious (visible bleeding and bleeding identified by imaging only).<br>Examples of overt bleeding include:<br>• Pseudoaneurysm<br>• Retroperitoneal hematoma seen on CAT scan<br>• Visible access site hematoma<br>**Actionable Bleeding** is more bleeding than expected for clinical circumstance needing increased level of care like<br>• hospitalization<br>• medical/surgical intervention<br>• transfusions<br>Thresholds for reporting procedural bleeding for SAVR procedure is bloody chest tube output > 600 mL within any 24-hour period and for TF-TAVR >100 mL total EBL (Estimated Blood Loss) from access site. These are suggested as guidelines for Site reporting of Bleeding events and clinical judgement should be used in reporting bleeding events.<br>**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.<br>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.<br>Note: Bleeding will be adjudicated per VARC-2 and BARC criteria. | Sponsor |
| CABG | Coronary artery bypass graft surgery is a procedure performed to bypass partially or completely occluded coronary arteries with veins (commonly Great/Small Saphenous veins) and/or arteries (commonly Internal thoracic/Mammary artery) harvested from elsewhere in the body, thereby improving the blood supply to the coronary circulation supplying the myocardium (heart muscle). | Sponsor/ 2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials |
| Cardiac Arrest | Cardiopulmonary arrest or circulatory arrest is a sudden stop in effective blood circulation due to the failure of the heart to contract effectively or at all. | Sponsor / STS |
| Cardiac Tamponade | Evidence of a new pericardial effusion associated with hemodynamic instability evident by:<br>1. Echo showing pericardial fluid and signs of tamponade such as right heart compromise, or<br>2. Systemic hypotension due to pericardial fluid compromising cardiac function | VARC-2 / STS |

| Term | Definition | Reference/ Justification |
|---|---|---|
| Cardiogenic Shock | Sustained (> 30 min) episode of systolic BP < 90 mmHg and/or cardiac index < 2.2 L/min/$m^2$ determined to be secondary to cardiac dysfunction, and/or the requirement for parenteral inotropic or vasopressor agents or mechanical support (e.g., intra-aortic balloon pump, extracorporeal circulatory support, ventricular assist device) to maintain BP and cardiac index above those specified levels | 2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials |
| Cardiopulmonary Bypass (CPB) | CPB is a form of extracorporeal circulation that temporarily takes over the function of the heart and lungs during surgery, maintaining the circulation and oxygen content of blood in the patient's body. | Sponsor |
| Cerebrovascular Disease | Cerebrovascular disease includes all disorders in which an area of the brain is temporarily or permanently affected by ischemia or bleeding and one or more of the cerebral blood vessels are involved in the pathological process. It includes:<br>• Stroke<br>• TIA<br>• Noninvasive or invasive arterial imaging test demonstrating >=50% stenosis of any of the major extracranial or intracranial vessels to the brain<br>• Previous cervical or cerebral artery revascularization surgery or percutaneous intervention<br>This does not include chronic (nonvascular) neurological diseases or other acute neurological insults such as metabolic and anoxic ischemic encephalopathy | STS |
| Congestive Heart Failure (CHF) | Heart failure develops when the heart due to an abnormality of cardiac function (detectable or not), fails to pump blood at a rate commensurate with the requirements of the metabolizing tissues or is able to do so only with an elevated diastolic filling pressure.<br>Diagnosis requires physician documentation or report of clinical signs and symptoms of heart failure like:<br>• Exertional dyspnea or Dyspnea at rest<br>• Orthopnea or Paroxysmal nocturnal dyspnea (PND)<br>• Acute pulmonary edema<br>• Fluid retention; or the description of rales, jugular venous distension<br>• Pulmonary edema on physical exam, or pulmonary edema on chest x-ray presumed to be cardiac dysfunction<br>A low ejection fraction alone, without clinical evidence of heart failure does not qualify as heart failure.<br>An elevated BNP without other supporting documentation should not be reported as CHF | STS |

| Term | Definition | Reference/ Justification |
|---|---|---|
| Coronary Obstruction | Angiographic or echocardiographic evidence of a new, partial or complete, obstruction of a coronary artery lumen or ostium, either by the valve prosthesis itself, the native leaflets, calcifications, or dissection, occurring during or after the TAVR procedure.<br>Mechanical coronary artery obstruction following TAVR includes:<br>• impingement of the coronary ostia by the valve support structure in the setting of suboptimal valve positioning and/or 'small aortic root' anatomy; OR<br>• displacement of native aortic valve leaflets towards the coronary ostia during TAVR | VARC-2/ STS/ Sponsor |
| Device | For the determination of device relationship, the study device consists of:<br>• Edwards CENTERA THV<br>• Edwards CENTERA Delivery System<br>• Edwards eSheath Introducer Kit<br>• Edwards Dilator Kit | Sponsor |
| Device (Valve) Fracture | The separation of any portion of the frame into two or more parts; as may be determined by radiography, computed tomography (CT), magnetic resonance imaging (MRI) or by direct examination. | Sponsor |
| Device Malfunction | The failure of a device to meet any of its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling of the device. The intended performance of a device refers to the intended use for which the device is labeled. | FDA, 21 CFR 803.3(m) |
| Device (Valve) Thrombosis | Any thrombus attached to or near an implanted valve that is an incidental imaging finding (echocardiography or CT etc.) and is asymptomatic, occludes part of the blood flow path, interferes with valve function (immobility of one or more leaflets etc.), or is sufficiently large to warrant treatment.<br>Prosthetic valve-associated thrombus identified at autopsy in a patient whose cause of death was not valve-related should not be reported as valve thrombosis | VARC-2 |
| Endocarditis | Endocarditis must meet at least one of the following:<br>• Fulfilment of the Duke endocarditis criteria<br>• Evidence of abscess, paravalvular leak, pus, or vegetation confirmed as secondary to infection by histological or bacteriological studies during a re-operation<br>• Findings of abscess, pus, or vegetation involving a repaired or replaced valve during an autopsy | VARC-2 [37] |
| EuroSCORE II | http://www.euroscore.org/calc.html | European System for Cardiac Operative Risk Evaluation |
| Explant | Removal of the investigational valve implant regardless of reason after the Index procedure is complete. | Sponsor |

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

| Term | Definition | Reference/ Justification |
|---|---|---|
| Hypertension | Hypertension is defined as a systolic blood pressure (SBP) of 140 mmHg or more, or a diastolic blood pressure (DBP) of 90 mmHg or more or taking antihypertensive medication. | Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) |
| Hypertrophic Cardiomyopathy (HOCM) | Cardiomyopathy is a term applied to a wide spectrum of cardiac diseases in which the predominant feature is poor myocardial function in the absence of any anatomic abnormalities.<br>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.<br>Cardiomyopathies are into three entities:<br>1. Dilated, characterized by ventricular dilatation and systolic dysfunction<br>2. Hypertrophic, characterized by physiologically inappropriate hypertrophy of the left ventricle<br>3. Restrictive, characterized by diastolic dysfunction, with a presentation often identical to constrictive pericarditis. | STS Congenital Heart Surgery Database Data Specifications |
| Hypotension | Hypotension is defined as a systolic blood pressure (SBP) lower than 90 mmHg, or mean arterial pressure (MAP) lower than 60 mmHg | Sponsor |
| Index Hospitalization (Index Procedure Hospitalization) | Index hospitalization is defined as the period of in-hospital stay for the prosthetic valve implant procedure. The period of Index hospitalization begins with date and time of admission for valve implant procedure and continues till the date and time the patient is discharged from the hospital where Index procedure is done. | Sponsor |
| Lung Disease, Severe | FEV1 < 50% predicted or currently on home oxygen | Sponsor |
| Mini-Mental State Examination (MMSE) | A questionnaire that is used extensively in clinical and research settings to measure cognitive impairment. | [38] |

| Term | Definition | Reference/ Justification |
|---|---|---|
| Modified Rankin Scale (mRS) | A commonly used scale for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke, as follows:<br>0 No symptoms at all<br>1 No significant disability despite symptoms; able to carry out all usual duties and activities<br>2 Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance<br>3 Moderate disability; requiring some help, but able to walk without assistance<br>4 Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance<br>5 Severe disability; bedridden, incontinent and requiring constant nursing care and attention<br>6 Dead | [39] |
| Mortality, All-Cause | **Cardiovascular mortality**<br>Any of the following criteria:<br>• Death due to proximate cardiac cause (e.g. myocardial infarction, cardiac tamponade, worsening heart failure)<br>• Death caused by non-coronary vascular conditions such as neurological events, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular disease<br>• All procedure-related deaths, including those related to a complication of the procedure or treatment for a complication of the procedure<br>• All valve-related deaths including structural or nonstructural valve dysfunction or other valve-related adverse events<br>• Sudden or unwitnessed death<br>• Death of unknown cause<br>**Non-cardiovascular mortality**<br>Any death in which the primary cause of death is clearly related to another condition (e.g. trauma, cancer, suicide). | VARC-2 |

| Term | Definition | Reference/ Justification |
|---|---|---|
| Myocardial Infarction | An acute ischemic event that is associated with documented and clinically significant myocardial necrosis<br>Any one of the following criteria meets the diagnosis for MI:<br><br>**Periprocedural MI** (≤ 72H after Index procedure)<br>New signs or symptoms of ischemia.<br>• Symptoms like chest pain or shortness of breath;<br>• Ischemic signs like ECG changes indicative of new ischemia [new ST segment elevation/depression of ≥1mm in ≥2 contiguous leads or new persistent left bundle branch block (LBBB)] or<br>• New pathological Q-waves in ≥2 contiguous leads or<br>• Imaging evidence of a new loss of viable myocardium or new wall motion abnormality<br>• AND Elevated cardiac biomarkers (Peak CK-MB rises post-procedure exceeding 5× the upper reference limit for CK-MB OR Peak troponin rises post-procedure exceeding 15× as the upper reference limit for troponin)<br>• If cardiac biomarkers are increased at baseline (>99th percentile), a further increase of at least 50% post-procedure is required AND the peak value must exceed the previously stated limit.<br><br>**Spontaneous MI** (Before Index Procedure or > 72 hours after the index procedure)<br>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:<br>• Symptoms of ischemia like chest pain or shortness of breath;<br>• 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<br>• Imaging evidence of a new loss of viable myocardium or new wall motion abnormality | STS |
| | **MI associated with sudden, unexpected cardiac death**<br>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<br><br>**Pathologic findings of an acute myocardial infarction** | |
| National Institutes of Health Stroke Scale (NIHSS) | The NIHSS is a method/tool developed by the National Institutes of Health used to gauge the severity of a stroke. NIHSS is a tool to help physicians objectively determine the severity of a stroke, help predict clinical outcomes and help guide management. | NIHSS/Sponsor |

<table>
<tr><th>Term</th><th>Definition</th><th>Reference/ Justification</th></tr>
<tr><td>New York Heart Association Classification (NYHA)</td><td>
<table>
<tr><th>NYHA Class</th><th>Functional Capacity</th></tr>
<tr><td>I</td><td>Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or anginal pain.</td></tr>
<tr><td>II</td><td>Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain.</td></tr>
<tr><td>III</td><td>Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea or anginal pain.</td></tr>
<tr><td>IV</td><td>Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.</td></tr>
</table>
</td><td>40</td></tr>
<tr><td>Paravalvular Leak (PVL)</td><td>Paravalvular or paraprosthetic leak is a complication associated with the implantation of a prosthetic heart valve whether traditional (surgical) or a transcatheter (TAVR) approach.<br>PVL refers to blood flowing through a channel between the structure of the implanted valve and cardiac tissue as a result of a lack of appropriate sealing</td><td>ESC</td></tr>
<tr><td>Peripheral Vascular Disease (PVD)</td><td>Includes peripheral arterial disease of upper and lower extremity, renal, mesenteric, and abdominal aortic systems, as follows:<ul><li>Claudication, either with exertion or at rest</li><li>Amputation for arterial vascular insufficiency</li><li>Vascular reconstruction, bypass surgery, or percutaneous intervention to the extremities (excluding dialysis fistulas and vein stripping)</li><li>Documented abdominal aortic aneurysm with or without repair</li><li>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</li></ul>Peripheral arterial disease excludes disease in the carotid, cerebrovascular arteries or thoracic aorta.<br>PVD does not include DVT.</td><td>STS</td></tr>
<tr><td>Pulmonary Hypertension</td><td>Pulmonary hypertension (PH), defined as a mean pulmonary arterial pressure ≥ 25 mmHg at rest in the presence of Left Atrial Pressure(LAP)/Wedge pressure ≤15 mmHg and is often characterized by a progressive and sustained increase in pulmonary vascular resistance that eventually may lead to right ventricular (RV) failure</td><td>ACC/Sponsor</td></tr>
<tr><td>Pre-existing Condition</td><td>A pre-existing condition is any chronic, recurring condition identified prior to enrollment in a clinical study, whether present at enrollment or not. A preexisting condition is not an adverse event unless it worsens as a result of the study treatment.</td><td>Sponsor</td></tr>
</table>

| Term | Definition | Reference/ Justification |
|---|---|---|
| Reintervention | Any intervention that repairs, alters or replaces a previously implanted or operated valve, which occurs after the completion of the valve implant procedure and the transfer to the procedure room. These interventions include:<br>• Balloon aortic valvuloplasty<br>• Surgical aortic valve replacement<br>• Valve in valve<br>• Paravalvular leak closure | STS/AATS |
| Serious Adverse Event (SAE) | Adverse Event that:<br>• Led to death,<br>• Led to serious deterioration in the health of the subject, that either resulted in<br>o a life-threatening illness or injury, or<br>o a permanent impairment of a body structure or a body function, or<br>o in-patient or prolonged hospitalization, or<br>o medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,<br>• Led to fetal distress, fetal death or a congenital abnormality or birth defect<br>• Significant medical event:<br>Important medical events that do not meet the above criteria may still be considered an SAE if they seriously jeopardize the subject and require immediate medical or surgical intervention to prevent one of the aforementioned outcomes. | ISO 14155-1:2011<br>FDA (21 CFR 312.32 (a) |
| Stroke / Transient Ischemic Attack (TIA) | **Diagnostic Criteria**<br>Acute episode of a focal or global neurological deficit with at least one of the following:<br>• change in level of consciousness<br>• hemiplegia, hemiparesis, numbness or sensory loss affecting one side of the body<br>• dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke<br>AND<br>No other readily identifiable nonstroke cause for the clinical presentation (e.g., brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences) to be determined by or in conjunction with designated neurologist | VARC-2 |

| Term | Definition | Reference/ Justification |
|---|---|---|
| | Confirmation of the diagnosis by at least one of the following#:<br>• Neurology or neurosurgical specialist<br>• Neuroimaging procedure (MR or CT scan)<br>• Clinical presentation alone<br><br>**Neurological event type classification:**<br>**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.<br>TIA**:** duration of a focal or global neurological deficit <24 h and neuroimaging does not demonstrate a new hemorrhage or infarct<br><br>**Stroke etiological classification:**<br>1. **Hemorrhagic**: an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage.<br>2. **Ischemic**: an acute episode of focal cerebral, spinal, or retinal dysfunction caused by an infarction of the central nervous system tissue<br>3. **Undetermined**: stroke with insufficient information to allow categorization as ischemic or hemorrhagic.<br><br>**Stroke severity classification:**<br>1. **Non-disabling**: a mRS score of <2 at 90 days or the last available clinical visit with evaluable data or one that does not result in an increase of at least one mRS category from an individual's pre-stroke baseline<br>2. **Disabling**: a mRS score of ≥2 at 90 days or the last available clinical visit with evaluable data and an increase of at least one mRS category from an individual's pre-stroke baseline | |
| Structural Valvular Deterioration (SVD) | Structural deterioration includes dysfunction or deterioration due to changes intrinsic to the valve, such as wear, fracture, calcification, leaflet tear, leaflet retraction, suture line disruption of components, prosthetic valve thickening, stenosis as determined by reoperation, autopsy or clinical investigation<br>SVD excludes infection/endocarditis or thrombosis | [41] |
| STS Adult Cardiac Surgery Risk Calculator | The Society of Thoracic Surgeons' risk models predict the risk of operative mortality and morbidity after adult cardiac surgery on the basis of subject demographic and clinical variables.<br>http://riskcalc.sts.org/stswebriskcalc/#/ | STS |
| Syncope | A fainting spell or loss of consciousness | STS |
| SYNTAX Score | An angiographic grading tool to determine the complexity of CAD.<br>http://www.syntaxscore.com/<br>http://ir-nwr.ru/calculators/syntaxscore/frameset.htm | |
| TAVR Risk Score | http://tools.acc.org/TAVRRisk/#!/content/evaluate/ | |

| Term | Definition | Reference/ Justification |
|---|---|---|
| THV-in-THV | An additional valve prosthesis is implanted within a previously implanted prosthesis because of suboptimal device position and/or function, during or after the valve implant procedure | VARC-2 |
| Transient Ischemic Attack (TIA) | See “Stroke / Transient Ischemic Attack (TIA)” | |
| 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 procedure room which are completed prior to subject transfer to a post-procedure recovery unit (e.g. Recovery Room, ICU/CCU, etc.<br>The valve implant procedure will be considered to have started when the first interventional access-related puncture (arterial) is established. The end of valve implant procedure is defined as date and time of vascular closure post-eSheath removal.<br>Performance of TEE does not by itself constitute start of procedure | Sponsor |
| Valve Malpositioning | **Valve migration**<br>• After initial correct positioning, the valve prosthesis moves upward or downward, within the aortic annulus from its initial position, with or without consequences<br>**Valve embolization**<br>• The valve prosthesis moves during or after deployment such that it loses contact with the aortic annulus<br>**Ectopic valve deployment**<br>• Permanent deployment of the valve prosthesis in a location other than the aortic root | VARC-2 |
| Vascular Injury | Injury to the vascular system that may be caused by the implanted valve or other accessories like guidewires, vascular sheaths, delivery catheters, or any balloons used for implanted valve dilatation etc. This includes arterial injuries like dissection, perforation, arteriovenous fistula, pseudoaneurysm formation, retroperitoneal hemorrhage, thromboembolism or incomplete arteriotomy closure and venous injuries like perforation, tears, or venous thrombosis including pulmonary embolism etc. and cardiac structural injuries like perforation or tearing of the major cardiac structures, pseudoaneurysm, cardiac tamponade or atrial septal defect etc. | VARC-2 / Sponsor |

## APPENDIX C. REFERENCES


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